Dosimetry at the Cellular Level of Kupffer Cells After Technetium-99m-Sulphur Colloid Injection

Isabelle Gardin, Nicole Colas Linhart, Anne Petiet, and Bernard Bok

Department of Biophysics, University X. Bichat, Paris, France

The radiation dose to Kupffer cells was estimated at the cellular level after intravenous injection of ^{99m}Tc labeled sulphur colloids in rats. The results were then compared with those obtained using macroscopic dosimetry. From the microscopy appearance observed using a "track" microautoradiographic method (MAR), it was shown that only 0.2% of the Kupffer cells were actually involved in the pinocytosis of radioactive colloids. For each electronic emission from ^{99m}Tc (Auger and internal conversion), the fraction of the emitted energy actually absorbed within the Kupffer cell was calculated using the values provided by Berger. About 15% of the total energy emitted by electrons was absorbed in 0.2% of the Kupffer cells. If these results are extrapolated to humans, the dose absorbed by the labeled cells can be estimated to be between 0.5 and 0.9 Gy/MBq. This represents about 15,000 times the average electron dose to the liver as estimated from macrodosimetric methods. In cases such as this one where an important distribution heterogeneity is expected, dosimetric estimations at a cellular level may be particularly useful.

J Nucl Med 1992; 33:380–384

Most dosimetric evaluations assume an homogeneous distribution (*1*) of the radionuclide within the organs of interest. Usually, the radiation dose delivered to human organs by electron-emitting radionuclides is estimated under the implicit assumption that the dose to every cell of the organ is the same as the integrated dose to the whole organ.

This estimation is of limited value if inhomogeneity is important or if the electron path is small as compared to radioactivity distribution. The nonuniformity expected in radioimmunotherapy invalidates the macroscopic approach. Radioimmunotherapy techniques aim to maximize the discrimination between healthy and affected tissues (*2,3*). In diagnostic nuclear medicine, inhomogeneity of radiopharmaceutical deposition is known. For example, ^{99m}Tc-labeled macroaggregated albumin used for lung scintigraphy is trapped in only one capillary out of a million (*4*). Therefore, the dose received by 8% of the lung cell population is 3 to 7500 times the average dose estimated by MIRD calculations (*5*).

The radiation dose delivered to individual radiosensitive cells has been the concern of several authors performing cell labeling (*6,7*), notably regarding the radiation dose delivered to individual radiosensitive cells, such as labeled lymphocytes with ^{111}In (*8*) and ^{99m}Tc (*9*). The de-excitation of ^{99m}Tc results in the emission of secondary electrons of various energies, most of them with short ranges (a few microns or less). Therefore the energy deposit is very localized.

In a previous study (*10*), we have shown that the pattern of radioactive distribution after ^{99m}Tc-sulphur colloid injection in the rat is very heterogeneous. Colloids are highly concentrated in Kupffer cells in the sinusoid area of the rat liver. It was also shown that very few Kupffer cells were able to endocytose colloids. The purpose of the present study was to estimate the radiation dose actually received by Kupffer cells following a ^{99m}Tc-sulphur colloid injection in the rat and to compare these results with those obtained by macrodosimetry. The microautoradiographic "tracks" method (MAR) (*11*) was used to determine the radioactivity distribution. Based on these results a simple model is proposed to derive the absorbed dose at the cellular level. Kupffer cells were considered as spherical source regions.

MATERIALS AND METHODS

Technetium-99m-Sulphur Colloid Solution Studies

A commercially available colloidal solution (TCK 1 Kit, CIS, Gif sur Yvette, France), currently used in human hepatic scintigraphy, was radiolabeled with ^{99m}Tc. Briefly ^{99m}Tc-heptasulphide (Tc_2S_7) was precipitated to produce a colloidal solution (*12*). The average diameter of the colloidal particles was 40 nm (*13*) and the labeling efficiency was always over 95% (*12*). A carotid catheter was placed in male Wistar rats, weighing 450 ± 50 g under Urethan anesthesia. A colloidal solution (1.4 ml), corresponding to a mass of 200 μg and to an activity of 17 MBq (495 μCi), as slowly injected.

The animals were divided into three groups and killed at 20 min, 1 and 6 hr, respectively, after the injection of the colloidal solution. The animals were exsanguinated and the liver immediately was fixed "in situ" by direct injection of 15 ml of saline formol into the carotid artery.

Microautoradiography

The track autoradiography technique applied to frozen tissue sections has been previously described (*10*). Briefly, after excision,

Received May 8, 1991; revision accepted Sept. 4, 1991.

For reprints contact: N. Colas Linhart, University X. Bichat, Department of Biophysics, 16, rue Henri Huchard, F-75018 Paris, France.

a piece of liver was refixed in saline formol for 30 min. Frozen sections, 10 μm thick were placed on gelatin-coated slides, dehydrated in 95% ethanol for 5 min, washed in distilled water and dried. A nuclear emulsion (K5 Ilford) was poured onto each slide to obtain a coating 25-μm thick. The exposure time varied between 14 and 26 hr.

The interactions between the electrons and the emulsion result in silver deposits all along their paths, which constitute the usual latent image. Since these elementary interactions are weak, the reduction of the silver salt may be incomplete (sublatent image) and would result after development in grey poorly visible spots. Therefore a gold activation (*14*) is necessary to transform the sublatent into a latent image (gold latensification). After this activation procedure, the preparation is developed and fixed.

Dosimetry

When using the method of absorbed dose calculations adopted by the MIRD Committee (*1*), one should describe absorbed dose distribution in terms of the specific absorbed fraction Φ. The absorbed dose rate, for a monoenergetic source of electron, is expressed as (*15*):

$$R(X,E_O) = A\ k\ n\ E_O\ \Phi(X,E_O), \qquad \text{Eq. 1}$$

where

$R(X,E_O)$ is the absorbed dose rate, in rad/sec at a distance X from the point-isotropic source.
$\Phi(X,E_O)$ is the fraction of the emitted energy that is absorbed at the distance X, per unit mass of the medium, in g^{-1}.
X is the distance from the source, in cm.
E_O is the initial energy of the emitted particles, in MeV.
n is the number of electrons of energy, E_O, emitted per disintegration.
A is the source activity, in Becquerel (dps).
$k = 1.6 \times 10^{-8}$ g.rad/MeV.

In the case of radionuclides like ^{99m}Tc, for which there are a number m of monoenergetic emissions, the formula becomes:

$$R(^{99m}Tc) = A\ k \sum n_i\ E_i\ \Phi_i(X_i,E_i). \qquad \text{Eq. 2}$$

The values of E_i (the energy of the emitted electron), n_i (the number of electrons) (*16*) and X_i (the range in unit density matter), as determined by interplation of Berger's values (*15*) are presented in Table 1.

In a previous study (*10*), we have shown that colloids are highly concentrated in a small number of Kupffer cells. These cells can be considered as spherical source regions. This simple model allows to calculate the fraction Φ of the emitted energy which is absorbed in the Kupffer cells. The results obtained from the data published by Berger are presented in Table 2. For $E_i <$ 0.5 keV, no data are provided by Berger. However the range of such electrons is very short (<0.2 μm). It can be considered that the whole energy is absorbed within the emitting cell itself and Φ_i is 1 g^{-1}.

Finally, the dose rate, R, is integrated versus time to obtain the dose, D. In the present case, uptake is assumed to remain constant once maximal uptake is reached.

For the photon dose, the classical dosimetry estimation for the liver was adopted. The range of the emitted photon (140 keV) is much greater than the cell diameter and therefore a homogeneous distribution can be assumed.

TABLE 1
Average Emission Spectra for ^{99m}Tc and Corresponding Range

E_i* (keV)	n_i*	X_i† (μm)
142.2	0.0011	192
140.0	0.0039	187
139.8	0.0035	186.5
137.7	0.0118	182
121.5	0.0088	148
119.4	0.0913	144
17.8	0.0055	5.3
15.4	0.0152	4.3
1.9	0.1093	<0.2
1.6	0.9860	<0.2
0.4	1.2359	<0.2

* From Bassano et al. (*16*).
† From Berger (*15*).

RESULTS

The radioactivity concentration within the liver was about 740 kBq/g (20 μCi/g), hence 12.5 MBq (340 μCi)/rat liver corresponding to 74% of the injected radioactivity. This uptake percentage was obtained 20 min after injection, remained stable in time and allowed us to use the physical half-life of ^{99m}Tc (6 hr) as the effective half-life of the radionuclide.

We have previously demonstrated the localization of ^{99m}Tc-colloids in Kupffer cells (*10*). Microscopic examination of the sections showed a heterogeneous uptake of radioactivity. Two uptake patterns were observed: high uptake areas (more than 100 tracks), concerning 0.13% of total number of Kupffer cells, and low uptake areas with few tracks (from 1 to 10), concerning 0.07% of Kupffer cells (Fig. 1). The number of total labeled cells were counted and the results are shown in Table 3.

Microautoradiographic results showed that the radioactive components were endocytozed by a small ratio of

TABLE 2
Value of Φ_i and $n_iE_i\Phi_i$ Obtained Within Radioactive Spheres 8 μm Diameter Filled with ^{99m}Tc

E_i (keV)	Φ_i (g^{-1})	n_iE_i (keV/dis.)	$n_iE_i\Phi_i$ (keV/g/dis.)
142.2	0.0074	0.156	0.001
140.00	0.0077	0.546	0.004
139.8	0.0077	0.489	0.003
137.7	0.0080	1.625	0.013
121.5	0.010	1.069	0.011
119.4	0.010	10.901	0.109
17.8	0.440	0.098	0.043
15.4	0.529	0.234	0.124
1.9	0.986	0.208	0.205
1.6	0.990	1.578	1.562
0.4	1	0.494	0.494
	Total	17.398	2.569

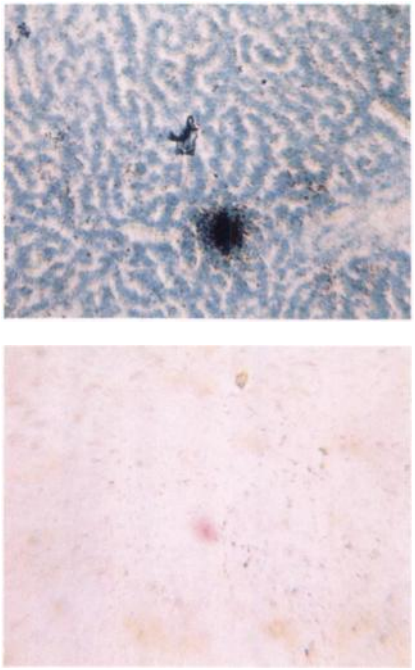

FIGURE 1. Results of ^{99m}Tc-colloids MAR in rat liver. (Top) Radioactivity uptake areas: more than 100 tracks. (Bottom) Phagocytosis of pink dye and ^{99m}Tc-colloids in Kupffer cells (1 to 10 tracks).

the Kupffer cells (0.2%) (Table 3). Since their radius is 4 μm (*17*) and their average number per gram of liver is $1.7.10^7$ (*18*), the Kupffer cells volume represents 6.10^{-3} of the total liver volume and the labeled cells represent approximately 10^{-5}. From these data, the average distance between two Kupffer cells showing tracks was computed to 193 μm. This length is slightly greater than the maximum electron path emitted by ^{99m}Tc atoms. Thus, the total radiation dose emitted by the electrons was deposited completely within or in the vicinity of the labeled Kupffer cells. There was no electron dose contribution emanating from the other cells.

The fraction $\Phi_i(d,E_i)$ (Equation 2, (*19*)) of the emitted energy absorbed in a sphere of diameter d between 2 and 14 μm for source energies E_O between 10 MeV and 0.5 keV has been estimated by Berger (*19*). The fraction $\Phi_i(d,E_i)$ is tabulated in Table 2 for d = 8 μm and for various values of E_i of ^{99m}Tc by interpolation of Berger's data. Products and sums of n_iE_i, $n_iE_i\Phi_i$ are also presented.

The approximate measure of cellular radioactivity was estimated between 20 and 32 Bq per cell. For the two uptake patterns we can calculate an upper and a lower dose. The upper value was calculated by assuming that 0.13% of the Kupffer cells had fixed the whole radioactivity. The lower value was calculated assuming a homogeneous distribution of the radioactivity in all the labeled cells (0.2%). These two values induce respectively an overestimation and an underestimation of the dose actually received by the Kupffer cells. The electron dose rate was therefore between 1.8 and 2.8 mGy/sec/injected MBq for radiolabeled Kupffer cells. The corresponding absorbed dose was between 54 Gy/MBq (20.10^2 Gy/mCi) and 89 Gy/MBq (33.10^2 Gy/mCi).

To extrapolate these results to humans, we used the ratio of rat-to-human liver weights assuming that the number of Kupffer cells in the rat liver/gram tissue is the same as that in the human liver and that their endocytotic capacity is also identical (*20*). In man, the corresponding absorbed electron dose to labeled cells is between 0.54 Gy/MBq (20 Gy/mCi) and 0.89 Gy/MBq (33 Gy/mCi).

In macroscopic dosimetry, the absorbed fraction of the emitted energy Φ_i is equal to 1 for electrons. As a result, the average dose provided by electrons of ^{99m}Tc is 38 μGy/MBq (0.14 rad/mCi) and by gamma radiation 54 μGy/MBq (0.20 rad/mCi). Thus, in hepatic scintigraphy, the macroscopic dose is 92 μGy/MBq (0.34 rad/mCi) (*21*).

TABLE 3
Ratio of Labeled Kupffer Cells

T* (min)	n†	Ac%‡
20	20	0.2
60	8	0.3
360	4	0.2

* Time between injection and sacrifice.
† Number of studied liver sections.
‡ Ratio of Kupffer cells that have ingested ^{99m}Tc-sulphur colloid versus total number of Kupffer cells.

DISCUSSION

Usual autoradiographic methods are based on the visualization of silver "grains" induced by the interaction between the radiation and the medium. These methods apply well to electronic radiations. When a gamma emitter such ^{99m}Tc is used, gamma rays are involved as well as electrons. Therefore, good images can be obtained at a macroscopic level. On the other hand, if microscopic observation is attempted, the signal/background ratio is poor and generally it is not possible to achieve a good autoradiographic picture, since the "grains" obtained are not easily differentiated from background noise.

The MAR technique described here makes use of a nuclear emulsion (with a high concentration of silver salt) which results in a noticeable absorption of high-energy (120-142 keV) conversion electrons as well as lower energy (15-21 keV) Auger electrons emitted during transition of ^{99m}Tc (*22*). The emulsion thickness and gold latensification of the sublatent image resulted in better visualization of the whole path of the electrons. The "track/background" or signal/noise ratio is much higher using the "track" method than using "grains" microautoradiography. This "track" method indeed suffers some intrinsic limitations. The length of the tracks may vary considerably according to the energy of the electrons. The origin of a track may be difficult to determine. It corresponds to the first detected interaction and not to the actual emission point. Only the horizontal projection is determined and the exact vertical position is not known even with a careful focus adjustment. The origin may be above or below the observed

slice. In addition, in many cases, accumulation of tracks results in clusters rather than individual tracks.

Furthermore, identification of the tracks is purely visual and thus depends on the observer. Results of tracks zone counting are shown in Table 3. However, variability of the results did not exceed 1% between two observers.

As a result, spatial resolution is of the same order of magnitude than the size of the cells. It is usually not possible to get access to a subcellular level. Therefore, the computation of the absorbed dose actually results in the determination of an average dose delivered to individual cells.

Previously, we have shown that tracks were localized only in Kupffer cells, and that localization of ^{99m}Tc-colloids was intracellular (*10*). In the present paper, we observed that only two Kupffer cells out of 1000 showed tracks (Table 3). This low ratio (0.2%) and the heterogeneous uptake (varying between few tracks to more than 100 tracks) could be explained by a marked variability in the endocytotic capacity between Kupffer cells, as already shown for other cells (*23*). Heterogeneous uptake of ^{3}H-albumin colloid by the Kupffer cells of mouse liver also have been observed by other authors (*24*).

Based on energy ranges, three classes of ^{99m}Tc electrons may be described (Table 1). The first is made of "high-energy" electrons (between 120 and 140 keV) with ranges from 140 to 190 μm, representing 85% of the total energy emitted by electrons. The second consists of "medium-energy" electrons (around 16 keV) with ranges similar to the radius of the Kupffer cell (4 μm), representing 2% of the total energy. The third is made of "low-energy" electrons (around 1 keV or less) with ranges below 0.2 μm, representing 13% of the total energy.

From Table 2, it appears that Φ_i, the specific absorbed fraction, is below 10^{-2} g^{-1} for high-energy electrons, but 0.5 g^{-1} for medium and near 1 g^{-1} for low energy electrons. Therefore, the relative contributions to the actual absorbed dose are 5.5%, 6.5% and 88%, respectively. Finally, about 15% of electron energy is absorbed in only 10^{-5} of the total human liver volume. This value may explain why electron dosimetry to these cells is $1.5.10^4$ times higher than the macroscopic electron dose and that the main contribution to the dose comes from "low energy" electrons.

The contribution of this third class may even be underestimated. If in addition, very low-energy electrons are taken into account, such as Coster-Kronig electrons (*5*), the dose contribution of this class to the labeled cells would be 90% instead of 88%.

In macroscopic dosimetry, the gamma contribution is 60% and the radiation dose due to photons is 54 μGy/MBq (0.2 rad/mCi). This value may be negligible for labeled Kupffer cells if compared to the electron dose, but contributes significantly to the irradiation received by the other liver cells.

Using another radiopharmaceutical (^{99m}Tc-microlite) Makrigiorgos et al. (*24*) found that macroscopic dosimetry underestimates the actual absorbed dose to some cells by a factor of 8 to 30. This apparent discrepancy with our evaluation might be explained by the differences in the ratio of the volume of the labeled cells to the total liver volume. This ratio was found to be between 0.001 and 0.01 in their paper, compared to 10^{-5} in ours. This may be due to differences in the biological behavior of the radiopharmaceuticals used by both groups (*25*).

The results of the present calculations may raise some questions regarding the possible radiobiological consequences of high radiation doses to Kupffer cells. Recent studies have shown that human Kupffer cells are not very radiosensitive (*26*). Furthermore, as the number of labeled Kupffer cells is very low (0.2% of the total Kupffer cells), the usefulness of hepatic scintigraphy as a diagnostic procedure is not modified.

CONCLUSION

Macrodosimetry is generally used to estimate the radiation hazard of a radionuclide within an organ. Only an average dose is obtained, but this method is widely accessible and the results are usually acceptable for that purpose. When the radionuclide distributes heterogeneously within the target, a better knowledge of its distribution becomes necessary for computation of the local dose.

Track microautoradiography allows for localization of ^{99m}Tc radiopharmaceuticals at the cellular level, visualization of radioactivity distribution, as well as determining the radiation dose to individual cells. Microdosimetry may be of major relevance for evaluating radiation dose at a cellular level and for studying radiobiological hazards after administration of a radiopharmaceutical.

This work confirms that tissue-averaged doses underestimate the dose received by certain cells within an organ. This heterogeneity in electron dose distribution is directly related to cell uptake heterogeneity and may be very high in some instances, as demonstrated here. For further studies using ^{99m}Tc radiopharmaceuticals, a microdosimetry model must be adapted according to the distribution pattern of the tracer used.

ACKNOWLEDGMENT

Supported in part by C.I.S. International Co. (Gif, France) grant F90041.

REFERENCES

1. Loevinger R, Berman M. A schema for absorbed-dose calculations for biologically distributed radionuclides. MIRD pamphlet No. 1. *J Nucl Med* 1968;9(suppl 1):7–14.
2. Prestwich WV, Nunes J, Kwok CS. Beta dose point kernels for radionuclides of potential use in radioimmunotherapy. *J Nucl Med* 1989;30:1036–1046.
3. Humm JL. Dosimetric aspects of radiolabeled antibodies for tumor therapy. *J Nucl Med* 1986;27:1490–1497.
4. Pham T, Wasnich R. I-131 sodium iodohippurate. In: *Practical nuclear pharmacy, second edition.* Honolulu: Banyan Enterprises, Ltd; 1981:72–74.

5. Makrigiorgos GM, Adelstein SJ, Kassis AI. Cellular radiation dosimetry and its implications for estimation of radiation risks. Illustrative results with technetium 99m-labeled microspheres and macroaggregates. *JAMA* 1990;264:592–595.
6. Hofer KG, Harris CR, Smith JM. Radiotoxicity of intracellular ^{67}Ga, ^{125}I, ^{3}H nuclear versus cytoplasmatic radiation effects on murine L 1210 leukaemia. *Int J Radiat Biol* 1975;28,3:225–241.
7. Makrigiorgos GM, Adelstein SJ, Kassis AI. Limitations of conventional internal dosimetry at the cellular level. *J Nucl Med* 1989;30:1856–1864.
8. Ten Berge RJM, Natarajan AT, Van Royen EA, Schellekens PTA. Labeling with indium-111 has detrimental effects on human lymphocytes: concise communication. *J Nucl Med* 1983;24:615–620.
9. Meignan M, Charpentier B, Wirquin E, Chavaudra J, Fries D, Galle P. Biological effects and irradiation dose induced in human lymphocytes in vitro by an intracellular radionuclide: ^{99m}Tc. *Radiation Res* 1983;94:263–279.
10. Hindie E, Colas-Linhart N, Petiet A, Bok B. Microautoradiographic study of technetium-99m colloid uptake by the rat liver. *J Nucl Med* 1988;29:1118–1121.
11. Barbu M, Colas-Linhart N, Bok B. Technetium-99m autoradiography of labelled white cells. *Acta Haemat* 1984;71:13–17.
12. Mikheev NB. Radioactive colloidal solutions and suspensions for medical use. *Atomic Energy Review* 1976;14,1:3–36.
13. Buchanan JW, Wagner HN. Regional phagocytosis in man. In: Reichard SM, Filkins JP, eds. *The reticuloendothelial system, volume 7B.* New York: Plenum Publishing Corp.; 1985:247–270.
14. Rechenmann R, Wittendorp. E. Some basic and practical aspects on the development of nuclear emulsions. *J. Microscopie et de Biologie Cellulaire* 1976;27,2–3:91–100.
15. Berger MJ. Distribution of absorbed dose around point sources of electrons and beta particles in water and other media. MIRD Pamphlet no. 7. *J Nucl Med* 1971;12(suppl 5):5–23.
16. Bassano DA, McAfee JG. Cellular radiation doses of labeled neutrophils and platelets. *J Nucl Med* 1979;20:255–259.
17. Krebs HA, Cornell NW, Lund P, Hems R. Isolated liver cells as experimental material. In: Lundquist F, Tigtrup N, eds. *Regulation of hepatic metabolism.* Symposium VI, May 22–24, 1973. Hunksgaard published Copenhagen; 1974:728–730.
18. Bouin A. Morphometry of liver sinusoidal cells. In: Wisse E, Knook DL, eds. *Kupffer cells and other liver sinusoidal cells.* Amsterdam: Elsevier North; 1977:61–82.
19. Berger MJ. Improved point kernels for electrons and beta ray dosimetry. Washington DC, US Department of Commerce, National Bureau of Standards. *NBSIR* 1973:73–107.
20. Kirn A, Steffan AM, Bingen A, Cinqualbre J, Gendrault JL. Isolement et culture de cellules de Kupffer humaines. *CR Acad Sci Paris* 1980;291.
21. Atkins HL, Cloutier RJ, Lathrop KA, et al. Technetium-99m sulphur colloid in various liver conditions. Report no. 3. In: Loevinger R, Budinger TF, Watson EE, eds. *MIRD primer for absorbed dose calculations.* New York. Society of Nuclear Medicine; 1988;43–45.
22. Lederer CM, Hollander JM, Perlman R. *Table of isotopes.* New York: Wiley; 1978:423–426.
23. Stavem P, Dahl O. Differences in phagocytic/adherence properties between normal neutrophils. *Scand J Haematol* 1984;33:212–214.
24. Makrigiorgos GM, Ito S, Baranowska-Kortylewicz J, et al. Inhomogeneous deposition of radiopharmaceuticals at the cellular level: experimental evidence and dosimetric implications. *J Nucl Med* 1990;31:1358–1363.
25. Praaning-Van Dalen DP, Knook DL. Quantitative determination of in vivo endocytosis by rat liver Kupffer and endothelial cells facilitated by an improved cell isolation method. *FEBS Lett* 1982;141:229–232.
26. Van Kaick G, Muth H, Kaul A, et al. Report on the German thorotrast study. *Strahlentherapie* 1985;80:114–118.

EDITORIAL

Does Nonuniformity of Dose Have Implications for Radiation Protection?

The decay of radionuclides following their administration to patients leads to the deposition of energy within various organs, tissues, cells, and subcellular fractions. The calculation of the absorbed dose has, therefore, been an important activity in nuclear medicine. Such dose estimates are used to determine the health risk(s) involved and the amount of radionuclide that should be administered to patients during routine procedures.

In this issue of *The Journal of Nuclear Medicine*, Gardin and her coworkers (*1*) have estimated the radiation dose to Kupffer cells in rats injected intravenously with ^{99m}Tc-labeled sulfur colloid. The absorbed dose was calculated at the microscopic (i.e., cellular) level, extrapolated to humans, and compared to the *mean* dose obtained at the macroscopic (i.e., organ or tissue) level. Using a microdosimetric approach, these authors have shown the dose absorbed by the *radiolabeled* Kupffer cells to be, in fact, approximately 15,000 times the average electron dose to the same cells as estimated by the conventional MIRD Schema (*2,3*), which assumes that the distribution of the radionuclide in organs/tissues of interest is uniform and that particulate radiations (betas and other electrons) are isotropic in their distribution and have ranges that are large relative to typical cell diameters (~10 μm). This report (*1*) confirms earlier studies (*4–21*), indicating that the nonuniform distribution of certain radiopharmaceuticals within organs/tissues/cells leads to a great deal of variability in the dose to individual cells and/or cell types within these organs/tissues. For example, it was recently demonstrated that while most of the cells within the lung (following the intravenous administration of ^{99m}Tc-labeled microspheres and macroaggregated albumin particles) receive a dose approximately one-fourth that assumed by conventional dosimetry, a small proportion of lung cells is exposed to a distribution of high doses, ranging from 3 to 7,500 times the mean dose, amounting to hundreds and thousands of cGy in some instances (*19*). In another case, the radiation dose to ^{99m}Tc-laden macrophages in human liver, lung, and spleen (after the intravenous administration of ^{99m}Tc-labeled albumin colloid) was found to be 10–60 times the MIRD estimate (*10,21*). In all such studies, the extent to which the average absorbed dose estimates deviate from the dose to individual cells was shown to depend mainly on the range of the emitted particles, the radiopharmaceutical in

Received Nov. 11, 1991; accepted Nov. 11 1991.
For reprints contact: Amin I. Kassis, PhD, Harvard Medical School, Dept., of Radiology (Nuclear Medicine), Brigham & Women's Hospital, Boston, MA 02115.