EDITORIAL

The MIRD Approach: Remembering the Limitations

Methods developed by the MIRD Committee (*1,2*) are used to calculate mean doses to models representing various organs and tissues in order to allow the evaluation of the risks associated with the administration of radiopharmaceuticals for medical procedures. The conventional MIRD technique as presently employed is commonly used to determine *average* radiation doses to specific organs and tissues. The dose to each cell is thus considered to equal the average organ or tissue dose.* This approach was adopted by the MIRD Committee as a practical solution for estimating the absorbed dose for structures which present a range of radioactivity distributions that are difficult to measure and to model. In reality, the tissue distribution of radionuclides used in nuclear medicine depends on the radiopharmaceutical. For example, nonuniformity of radionuclide distribution would be expected to be greater for nonspecific carrier molecules such as ^{99m}Tc-labeled macroaggregated albumin than for ^{99m}Tc-HMPAO or for radionuclides in their free ionic form such as ^{201}Tl-chloride or ^{67}Ga-citrate. Consequently, the dose to individual cells within tissues/organs will differ according to the radiopharmaceutical.

This editorial attempts to address the adequacy of the average dose for particulate radiations and the possible consequences and biologic implications of its use. Recent experimental data and dosimetric calculations for several radiopharmaceuticals have indicated great variability in the dose to individual cells within an organ (*3–12*). In general, such variation occurs whenever the range of the emitted radiation is comparable to or shorter than the regional nonuniformities of radiopharmaceutical localization. In fact, dose nonuniformities occur regardless of the range of the particles (inverse square law). The degree to which the dose to an individual cell deviates from the mean dose depends on several factors. Among these are the particular characteristics of the carrier molecule (e.g., size and affinity to certain cellular components), the extent of radionuclide concentration in specific regions/cells throughout the tissue of interest, the subcellular localization of the radionuclide, and the fraction of the tissue volume occupied by the radiopharmaceutical (*3–20*). For example, the radiation dose to cells that concentrate ^{201}Tl is substantially higher than the MIRD mean dose (*4,5*); that to ^{99m}Tc-laden macrophages in human liver, lung and spleen after the intravenous administration of ^{99m}Tc-labeled albumin colloid is 10–60 times the MIRD estimate (*11,12*). A similar calculation (*10*) for ^{99m}Tc-labeled microspheres and macroaggregated albumin found that the doses to individual lung cells varied substantially from the mean dose estimate to the lung. Most of the cells (92%) were shown to receive a dose approximately one-fourth that assumed by conventional dosimetry, while the remaining cells (8%) received a distribution of high doses, ranging from 3 to 7,500 times the mean dose (*10*). Naturally, the extent to which the average absorbed dose deviates from the dose to individual cells will depend mainly on the nonuniformity of radionuclide distribution and the range of the emitted particles.

In the preceding paper by Robertson et al. (*21*), the average radiation absorbed dose from indium-labeled blood platelets to selected organs and structures has been calculated. However, the studies presented above (*9–12*), and the realistic expectation of nonuniform spatial distribution of radioindium-labeled platelets within tissues, indicate that at least two problems may arise from the dose averaging. The first problem is concerned with the self-absorbed (i.e., platelet) dose and the biological effects thereof, an issue that has been visited previously by several authors (*3–6,9–20, 22,23*) but not yet resolved. The second problem relates to the dose to those cells that are in the immediate vicinity of the radiolabeled platelets. Here again, such cells would be expected to receive doses that are considerably higher than the average dose.

What is the significance of the high individual cell dose expectations? Presently, it is difficult to relate such estimates to radiation risk or to assess their implications for radiation protection. This is partly because: (a) the relative sensitivity of various cell types within an organ is variable and (b) thus far it has not been possible to detect the effects of the radiation in the few cells that receive high doses. Because of the low *average* doses, the administration of radiopharmaceuticals to patients continues to be considered safe in terms of radiation protection. There are no epidemiological data to contradict this.

Finally, it is important to note that while the MIRD schema is intrinsically capable of accommodating complex geometry, including models at the cellular level, average energy deposition is presently calculated using a model in which: (a) nonuniformities in activity distribution are ignored, (b) the ranges of particulate radiations (beta particles and other electrons) are often large relative to cell diameters and (c) relatively simplistic S-value models are employed. To obtain S values that are appropriate for dose

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* This editorial uses customary terminology in speaking of dose to cells, tissues, and organs, even though it is recognized that dose can be calculated only for *models* of cells, tissues, and organs. As the word is used here, the model is the totality of the assumptions used in the dose calculations.

calculations at the cellular level, realistic biological assumptions or in-vivo data of radionuclide suborgan/cellular distributions and absorbed fractions reflecting actual particle ranges are required. The MIRD Committee, which recognizes the significance of calculating cellular as well as organ doses, hopes that this editorial will provide the scientific community with the incentives to: (a) develop internal dosimetry calculations based on improved activity distribution measurements of human samples, (b) explore the risks of mutagenesis at the cellular level as a function of absorbed dose and (c) design epidemiological studies that would specifically address the possible biological consequences of dose nonuniformity.

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