

The MIRd Perspective 1999

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Nuclear medicine procedures provide valuable diagnostic information and noninvasive approaches to therapy. However, as with any medical procedure, the risks and benefits must be weighed. The radiation absorbed dose is an essential part of assessing the risk from diagnostic radiologic procedures and predicting efficacy in radiation therapy. The generalized MIRd schema was formulated to facilitate the calculation of radiation absorbed dose from distributed sources of radioactivity (1). This article provides a historical account of the events leading to the development of the MIRd schema, a concise presentation of the formalism and its early application to organ dosimetry as elaborated in MIRd Pamphlet No. 11 (2) and a discussion on the general applicability of the formalism for dosimetry at all spatial levels ranging from organ to cellular dimensions. This article also introduces four new MIRd Pamphlets that will appear in upcoming issues of *The Journal of Nuclear Medicine*: MIRd Pamphlet No. 14 Revised: A Dynamic Urinary Bladder Model for Radiation Dose Calculations (3); MIRd Pamphlet No. 15: Radionuclide S Values in a Revised Dosimetric Model of the Adult Head and Brain (4); MIRd Pamphlet No. 16: Techniques for Quantitative Radiopharmaceutical Biodistribution Data Acquisition and Analysis for Use in Human Radiation Dose Estimates (5); and MIRd Pamphlet No. 17: The Dosimetry of Nonuniform Activity Distributions—Radionuclide S Values at the Voxel Level (6). These pamphlets are part of the MIRd Committee's ongoing efforts to provide new tools for a variety of radionuclide dosimetry applications covering topics such as dosimetry for dynamic masses, patient-specific organ dosimetry, dosimetry for small structures within organs of the body (i.e., suborgan dosimetry), three-dimensional dose distributions, cellular dosimetry and acquisition of quantitative data on pharmacokinetics.

THE MIRd SCHEMA

Origin of the MIRd Schema

Manmade radionuclides became available for medical use in the late 1930s and the 1940s, and methods of tissue absorbed dose calculation began to be developed from the very beginning. In 1948, Marinelli et al. published three articles that summarized radionuclide dosimetry up to that time and laid out a general approach that was immediately widely accepted (7–9). These papers marked the beginning of modern radiation dosimetry in nuclear medicine.

The approach of Marinelli et al. assumed that radiations were of two kinds: beta particles, which deposit their energy at the spot where they originate, and gamma rays, which deposit their energy in tissue over extended distances. For the latter, Marinelli et al. adapted the method of calculation that had been developed for radium brachytherapy sources to internally distributed radionuclides. That is, they characterized each unfiltered point source in terms of its exposure rate (in roentgens) in air. They assumed exponential absorption and evaluated a geometrical factor by integrating over various volumes. This was the standard approach at that time; the contribution of Marinelli et al. was to systematize the relevant equations and to summarize the relevant information on some 32 radionuclides of interest in medicine, rather than to break new ground.

At that time, nuclear medicine was a healthy infant. In 1950, an article set out to review, in 70 pages, the entire field of nuclear medicine (10). That article, published just 3 yr after the Marinelli et al. articles, listed some 44 radionuclides of interest in medicine.

In the decade after 1948, there were many contributions to the dosimetry of administered radionuclides, with original work and important summaries by some of the great names in medical physics: L.H. Gray and W.V. Mayneord in the United Kingdom and R.D. Evans, G. Failla, L.D. Marinelli and E.H. Quimby in the United States, to name just a few. All these contributions followed the basic Marinelli et al. approach and extended it in one respect or another.

In 1956, the situation to that date was summarized and elaborated in two chapters in *Radiation Dosimetry* by Hine and Brownell (11,12). In these chapters, an attempt was made to extend the viewpoint of Marinelli et al. to cover all the physical problems of the many internally distributed radionuclides that were by then available; this attempt necessitated a certain amount of additional detail. It resulted in a somewhat elaborate set of equations, some for point beta-particle sources, some for point gamma-ray sources, some for distributed beta-particle sources and still others for distributed gamma-ray sources. Each of these equations had two quite different forms, one for dose and another for dose-rate. For reasons related to the sizes of various tissues and the penetrating abilities of various radiations, some gamma rays and x-rays were treated like beta particles and some beta particles were treated like photons. To cover all cases, it was necessary to provide separate equations for point, line, surface and volume sources and also separate equations for dose to a point and mean dose to lines, surfaces and volumes. Many of these equations made use, explicitly or implicitly, of the well-known Mayneord reciprocity theorem, which appeared in several forms (13,14). Finally, the time-dependent terms—which are necessarily independent of radiation type—were given separately for each radiation type. The result was a redundant set of equations that defied easy

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presentation. It appeared at that time to be impossible to make the treatment of internal dose computations both complete and simple.

An important contribution to the Marinelli et al. approach was made in 1964 and 1965 in two articles by Ellett et al. (15,16). They defined the absorbed fraction as the fraction of the energy emitted by a source of gamma rays that is absorbed in a specified volume of tissue. They performed Monte Carlo calculations for photon sources of various energies and for target volumes of various sizes and shapes. This was the first application of Monte Carlo methods to radionuclide dosimetry calculations. The importance of the work of Ellett et al. was twofold: the new concept of the absorbed fraction simplified the dosimetry equations, and the Monte Carlo calculations made unnecessary the assumption of exponential absorption and, with it, the limitation of the calculations to volumes that could be analytically integrated.

Stimulated by the work of Ellett et al. (15,16), Loevinger and Berman recognized that the equations for internal dosimetry could be formulated in general terms, independent of the characteristics of particular radiations. These individuals were recruited into the newly formed Medical Internal Radiation Dose Committee, and in 1968, the original MIRD schema was published as MIRD Pamphlet No. 1 (17).

Derivation of the MIRD Schema

Ellett et al. (15,16) used a simple equation to relate the absorbed fraction to the absorbed dose, and that equation forms a convenient starting point in our discussion of the MIRD method of dose calculation. The Ellett et al. (15,16) equation for absorbed dose from a gamma ray emitter can be written in current MIRD notation (1) as follows:

$$\bar{D}_\gamma(v \leftarrow s) = \tilde{A}_s \sum_i \frac{\Delta_i \phi_i(v \leftarrow s)}{m_v}, \quad \text{Eq. 1}$$

where $\bar{D}_\gamma(v \leftarrow s)$ is the mean absorbed dose to volume v from radioactivity in source s that emits gamma-rays. The symbol A_s represents the activity in source s , and the symbol \tilde{A}_s represents the time integral of the activity for the time interval of interest and is called, in MIRD terminology, the cumulated activity. Thus, \tilde{A}_s represents the total number of nuclear transformations in source s during the time of interest. The symbol Δ_i represents the mean energy of radiation type i emitted per nuclear transformation; values of Δ_i are tabulated for more than 200 radionuclides (18). The symbol ϕ_i represents the absorbed fraction for radiation i , and the argument of ϕ_i indicates that it is the fraction of the energy emitted by source s that is absorbed in target volume v . Finally, m_v is the mass of target volume v .

There is no reason why this Ellett et al. equation must be limited to gamma rays. Thus, the subscript gamma can be dropped to obtain:

$$\bar{D}(v \leftarrow s) = \tilde{A}_s \sum_i \frac{\Delta_i \phi_i(v \leftarrow s)}{m_v}. \quad \text{Eq. 2}$$

This equation gives the mean absorbed dose to target volume v from all the radiations of whatever kind emitted by any source region s . This is a rather general result, but there is one limitation: it applies only to target regions that are volumes because the absorbed fraction applies only to volume targets. To generalize this result so that it can apply to any target region, a point, a line, a surface or a volume, we define the specific absorbed fraction as the quotient of the absorbed fraction and the mass of the target volume:

$$\Phi(v \leftarrow s) = \frac{\phi(v \leftarrow s)}{m_v}. \quad \text{Eq. 3}$$

Consequently, the specific absorbed fraction is simply the mean fraction of the energy emitted by source s that is absorbed per unit mass in target volume v . Suppose now the target region s is a point. Imagine a small volume v enclosing that point, and suppose that the specific absorbed fraction applies to that small volume. One may also imagine that the volume v becomes smaller and smaller. The absorbed fraction in the numerator and the mass m_v in the denominator become vanishingly small, but the quotient on the right remains finite and reaches a limiting value in the manner of the differential calculus. Thus, the specific absorbed fraction has a meaningful value at a point or at any other target, because the same argument can be applied to a line or a surface. Then the specific absorbed fraction is perfectly general and, using MIRD notation (1), one may write the specific absorbed fraction in the form:

$$\Phi(r_k \leftarrow r_h)$$

as the mean fraction of the energy absorbed per unit mass at any target region r_k from any source region r_h .

The mean dose to a target can be written in the more general form:

$$\bar{D}(r_k \leftarrow r_h) = \tilde{A}_h \sum_i \Delta_i \Phi_i(r_k \leftarrow r_h). \quad \text{Eq. 4}$$

Equation 4 is the full MIRD equation for dose to the target region r_k from radiations i emitted by source region r_h . This equation is very general. Because no assumptions were made except those implied in defining the quantities, no restrictions are placed on the source or target regions or the surrounding medium as to size, shape and position. Furthermore, no assumptions were made regarding the distribution of radioactivity in the source regions or the types of radiations emitted by the source.

Integral and Rate Equations

It is convenient to note first the relationship of these integral equations to dose-rate equations. If we assume—as is almost always done in practice—that the activity does not redistribute in the source organ and that the source and target organs have a fixed mass, then the absorbed fraction ϕ and the specific absorbed fraction Φ are not functions of time. Only two variables remain as functions of time, absorbed dose on the left and cumulated activity on the right of each equation. By differentiating with respect to time, we convert dose to dose rate and cumulated activity to activity, and rate equations replace the integral equations. Because the rate equations and the integral equations can be so readily converted from one to the other, it is unnecessary in a general discussion to show both.

Time-Dependent Mass

In some instances, the mass of the tissue may not remain constant during the period of irradiation. For example, the organ masses within a fetus can grow substantially before the radioactivity in the fetus has completely decayed. The bladder volume gradually increases between voids and decreases abruptly during a void (3). Similarly, tumor masses may undergo growth or shrinkage during radionuclide therapy. In these instances, a more general form of Equation 4 is needed to calculate the mean absorbed dose (19):

$$\bar{D}(r_k \leftarrow r_h) = \sum_i \Delta_i \int \frac{A_h(t) \phi_i(r_k \leftarrow r_h, t)}{m_k(t)} dt. \quad \text{Eq. 5}$$

Note that the absorbed fraction ϕ_i is also time-dependent because it is a function of the mass and dimensions of the source and target regions.

Residence Times and S Values

The residence time is defined as the cumulated activity in source region r_h per unit administered activity:

$$\tau_h = \frac{\tilde{A}_h}{A_0}, \quad \text{Eq. 6}$$

where A_0 is the administered activity. Substituting this expression into the full MIRD Equation 4, one obtains:

$$\frac{\bar{D}(r_k \leftarrow r_h)}{A_0} = \tau_h \sum_i \Delta_i \Phi_i(r_k \leftarrow r_h), \quad \text{Eq. 7}$$

and for volume targets, one obtains:

$$\frac{\bar{D}(r_k \leftarrow r_h)}{A_0} = \tau_h \sum_i \frac{\Delta_i \phi_i(r_k \leftarrow r_h)}{m_k}, \quad \text{Eq. 8}$$

Either of these two equations may be used, depending on whether the absorbed fraction or the specific absorbed fraction has been tabulated for the model of interest. The residence time has been introduced because dose estimates for a broad category of models are wanted in terms of absorbed dose per unit administered activity. The physical interpretation of the residence time is somewhat abstruse and is discussed in the *MIRD Primer* (1), but the definition in Equation 6 is adequate for these purposes. Because the cumulated activity has the dimensions of activity multiplied by time, the residence time has the dimension of time.

Equations 7 and 8 are often used, but they are unnecessarily detailed for routine calculations with established physical models. They have been simplified by Snyder et al. (2) by defining a new quantity:

$$S(r_k \leftarrow r_h) = \sum_i \Delta_i \Phi_i(r_k \leftarrow r_h) = \sum_i \frac{\Delta_i \phi_i(r_k \leftarrow r_h)}{m_k}. \quad \text{Eq. 9}$$

Substituting these expressions for S into Equations 7 and 8, one obtains the equation:

$$\frac{\bar{D}(r_k \leftarrow r_h)}{A_0} = \tau_h S(r_k \leftarrow r_h). \quad \text{Eq. 10}$$

Using the definition of residence time given in Equation 6, it is apparent that S is the mean absorbed dose per unit cumulated activity, commonly referred to as the "S value." Because the target organ k can receive radiation from more than one source, the dose is summed over all source organs h by writing:

$$\frac{\bar{D}(r_k)}{A_0} = \sum_h \tau_h S(r_k \leftarrow r_h). \quad \text{Eq. 11}$$

This is the equation most commonly used in MIRD dose calculations.

The utility of the MIRD dosimetry formalism lies in its simplicity and generality. Much of its simplicity lies in the clear separation of the physical aspects of the dose calculation (embodied in the S values) from the temporal aspects of the dose calculation (embodied in the residence times). The physical aspects include all of the physical assumptions made in the model, as well as the radiations emitted by the radionuclide and

their deposition of energy in the components of the model; the temporal aspects include the physical decay of the radionuclide and the biologic kinetics of the radionuclide in the various source organs. The generality of the MIRD formalism lies in the fact that no assumptions have been made regarding the composition and geometry of the source and target regions or the distribution of activity within the source regions. The S values can be calculated for any geometric model of sources and targets. Biokinetic data consistent with the degree of spatial detail required by the physical model must be obtained. Accordingly, given an appropriate model and set of biologic data, the MIRD schema can accommodate a wide variety of radionuclide dosimetry applications, including organ dosimetry, tumor dosimetry and cellular dosimetry, with either uniform or nonuniform activity distributions (20).

DOSIMETRY MODELS AND THE MIRD SCHEMA

General Assumptions in Physical Models

Implicitly assumed in dosimetry models based on the MIRD schema is that anatomic regions can be represented by a mathematical anatomic model that specifies the size, shape, position, composition and density of each region. Each region, however small (e.g., cell or organ), is considered to be homogeneous, and the mean absorbed dose to the target region is assumed to be an important physical quantity for quantifying its response to radiation. Thus, the dose gradient within each target region and microscopic fluctuations in energy imparted per unit mass are both ignored. The source and target regions, however, can be made as small as desired so that a large region (e.g., tumor and organ) can effectively be broken up into a sufficient number of source and target regions to obtain information on dose gradients. These can be used, in turn, to obtain dose-volume histograms (6).

General Assumptions in Temporal Models

In addition to the physical assumptions summarized above, absorbed dose calculations necessarily require assumptions regarding the temporal aspects of the calculation; namely, the specification of the residence times for the various source regions. Specifically, assumptions are made when quantitating the radioactivity in the various source regions (21). When the activity in a given source region cannot be directly quantitated, kinetic models are often used to project the uptake and clearance pattern based on information that can be obtained from neighboring regions (22). Kinetic models used to describe the ongoing processes of uptake and removal of metabolites are often highly sophisticated models involving large numbers of compartments. Determination of the equations describing compartment activity as a function of time is often a considerable problem. For dosimetry purposes, such models are generally reduced to three or four compartments. When the compartments are assumed to coincide with body organs, the kinetic model can be used directly in the dose calculation. Often, however, some of the compartments represent distributions within the body without identification with specific tissues; then, for dosimetry purposes, suitable fractions of these compartment activities must be assigned to model body organs, i.e., to volumes within the anatomic model. This is generally an approximate and, perhaps, subjective assignment.

Accuracy of Model Absorbed Doses

In light of the generalizations used in dose estimation, one may ask whether absorbed dose calculations using the limited biokinetic data generally available and estimated S values are accurate and reliable with respect to the model and, separately, with respect to the actual tissue regions of interest. First, with

respect to the model. The model is the totality of all the assumptions, physical and temporal, that enter into the dose calculation. The general assumptions implicit in MIRD absorbed dose calculations for radionuclides can be broken down into three categories:

1. Mean absorbed dose to a region is an important physical quantity for predicting response of that region to radiation. Dose gradients within each region and microscopic fluctuations in energy imparted per unit mass are ignored;
2. Anatomic aspects can be represented by a mathematical anatomic model that specifies the size, shape, position, composition and density of each region. Each region is uniform and homogeneous; and
3. Kinetic aspects can be represented by a mathematical model that describes the activity within each compartment and the movement of activity between compartments. The activity within each compartment can be assigned to one or more anatomic regions and is uniformly distributed within each region.

Bearing in mind all the assumptions, one can ask: How precise is the calculation of dose with respect to the model? Once a model has been fixed, the calculation can in principle be made as precise as desired. In practice, the limit of precision is usually set by the s.d. of the absorbed (or specific absorbed) fractions, due to practical limitations of the Monte Carlo method of calculation. The coefficients of variation may vary from a fraction of a percent to 50% or more for small target regions at sites distant from the source (23). Thus, in general, a reasonably high degree of precision can be obtained for the absorbed fractions.

The regions of a dosimetry model are given names corresponding to anatomic regions (e.g., cell nucleus, kidney and so on), and this tends to blur the distinction between model and anatomical object. One may question the accuracy of the calculated dose with respect to a particular anatomical region or with respect to that anatomical region within a population (e.g., cells or patients). It is not necessary to dwell on the inherently crude nature of the anatomic and kinetic models or the approximate nature of the many assumptions that go into any model. Given the inevitable oversimplification of a fixed model design relative to the actual patient anatomy and physiology, it appears that accuracy to a factor of two is about all that can be expected when estimating doses for individual patients, given the natural variations in the physical and temporal aspects of the source and target regions (1,2,6). However, as more patient-specific information is made available by direct measurement and incorporated into individualized model dosimetry, the accuracy of absorbed dose calculations has shown improvement as evidenced by a better correlation between dose and clinical response (24,25).

TRADITIONAL APPLICATION OF THE MIRD SCHEMA

Although the MIRD formalism is general, historically, the MIRD Committee has been principally concerned with organ dosimetry for administration of diagnostic radiopharmaceuticals in humans. The majority of the MIRD Committee organ dose estimates have traditionally been made using the S tables in MIRD Pamphlet No. 11 (MIRD 11) (2). These S values are based on the 70-kg adult anthropomorphic model and specific absorbed fractions given in MIRD Pamphlet No. 5 Revised (MIRD 5R) (23). The S values in MIRD 11 are given for about 20 target-organ and source-organ pairs for 120 radionuclides. As a result, organ absorbed dose calculations based on the

MIRD 5R model are simple to perform, provided residence times are available.

Physical and Temporal Assumptions in MIRD 11

Several assumptions were adopted in the calculation of the organ S values tabulated in MIRD 11 (2), which set limitations on their applicability. Among the assumptions is that source activity is uniformly distributed in a homogeneous medium that is sufficiently large that there are no edge effects, so that one has what is called a uniform isotropic model. One characteristic of the uniform isotropic model is that the specific absorbed fraction is independent of which region is designated source and which target. This is conveniently expressed in the form:

$$\Phi(r_k \leftarrow r_h) = \Phi(r_h \leftarrow r_k) = \Phi(r_k \leftrightarrow r_h), \quad \text{Eq. 12}$$

where the double-ended arrow indicates that the source and target can be interchanged in evaluating the specific absorbed fraction. This reciprocity theorem played an important role in obtaining many of the S values in MIRD 11. The MIRD 5R model is, of course, finite in its dimensions, but it has been shown (26) that the reciprocity principle is good to ~10% in that model, except for calculations involving bone. Human studies have shown good agreement with these findings (27).

Like all dosimetry models based on the MIRD schema, MIRD 11 implicitly assumes that anatomic aspects can be represented by a mathematical anatomic model that specifies the size, shape, position, composition and density of each region. Each model region corresponding to an organ is assumed to be homogeneous. The mean absorbed dose to an organ is assumed to be the appropriate physical quantity for quantifying its response to radiation, and therefore, the relative biologic effectiveness (RBE) of the different radiations emitted by the radionuclides is neglected in the determination of the model organ S values.

A major simplification in MIRD 11 is the division of the nuclear radiations into two broad categories: penetrating radiations and nonpenetrating radiations. Beta particles and electrons are taken to be nonpenetrating; that is, their initial kinetic energy is assumed to be absorbed within the source region in which they are emitted. Thus, nonpenetrating radiations have absorbed fractions equal to unity for the source organ and zero elsewhere. This approximation is adequate for the organs modeled in the MIRD 5R model. Absorbed fractions for low-energy photons (<10 keV) are approximated as described in MIRD 11. Briefly, when the source and target are not the same, the values of ϕ are extrapolated linearly to zero as energy decreases to zero. When the source and target regions coincide, the value of ϕ is extrapolated linearly to unity as the energy decreases to zero. Photons of energy above 10 keV are taken to be penetrating; the absorbed fractions were previously assessed via Monte Carlo transport within the MIRD 5R anthropomorphic model (2,23,28).

As noted earlier, absorbed dose calculations require assumptions regarding the temporal aspects of the calculation. These aspects of the dose calculation are discussed extensively in MIRD Pamphlet No. 16 (5), appearing in the February issue of *The Journal of Nuclear Medicine*. It suffices to say that numerous specific assumptions regarding the physical and temporal aspects of the dose calculation are always necessary. As a single example, some of the specific assumptions used in MIRD Dose Estimate Report No. 13 for ^{99m}Tc bone agents (29) are listed here:

1. A four-compartment kinetic model is adopted;
2. First-order kinetics is assumed between compartments;

3. Rate constants are calculated from blood and urine samples;
4. Plasma and extracellular fluid (ECF) activity is in a steady state 30 min after administration;
5. Total body water is 600 ml/kg for men and 500 ml/kg for women;
6. 43.3% of the body water is ECF;
7. 7% of the body water is plasma;
8. Half of the bone activity is trabecular and half is cortical;
9. Bladder is first emptied at 2 hr and then at 4.8-hr intervals; and
10. Residence time in remainder of body = residence time for blood and ECF.

There are other specific assumptions, but the list above is adequate to illustrate that every internal dose calculation is based on many assumptions, both general and specific.

Accuracy of MIRD 11 Absorbed Dose Estimates

Given the large number of assumptions inherent in MIRD 11 dosimetry calculations, how accurate is the calculated dose with respect to a particular patient or with respect to a class of patients? As mentioned earlier, the anatomic and kinetic models are only crude approximations. Hence, it appears that accuracy to a factor of two is about all that can be confidently claimed in general for dose calculations using non-patient-specific biokinetic data and MIRD 11 S values (1,2,6).

If one is skeptical of the relationship between the MIRD 11 model and the patient, of what use are these radiopharmaceutical dose calculations? Their most important function is to provide a dose estimate adequate to assure us that a specified class of patients will not be harmed in diagnostic studies and will at the same time satisfy regulatory requirements. The MIRD Committee and the International Commission on Radiation Units and Measurements (30) believe that MIRD 11-type dose calculations provide this assurance.

Sometimes information more quantitative than simple assurance is required from these elaborate calculations. For example, in therapeutic nuclear medicine the absorbed dose to various tissues is required to predict biologic response. However, the correlation of MIRD 11 dose calculations with normal tissue response is in the weak to moderate range for patients undergoing radioimmunotherapy (25,31). These patients frequently have organ masses that differ markedly from those assumed in the MIRD 5R model, thus leading to errors in the absorbed dose estimates. Under these circumstances, substantial improvement in the accuracy of absorbed dose calculations can be achieved by explicitly determining organ volumes using CT or MRI and applying simple corrections to the MIRD 11 S values used for calculating the self-dose components of the organ absorbed doses. For instance, the self-dose to an organ from a radionuclide that primarily emits nonpenetrating radiations can be corrected for mass as suggested in MIRD 11 (2):

$$S(\text{patient organ} \leftarrow \text{patient organ}) = \frac{m(\text{model organ})}{m(\text{patient organ})} S(\text{model organ} \leftarrow \text{model organ}).$$

Corrections can also be applied for the self-doses from penetrating radiations, as described in MIRD 11 (2). When these corrections are applied and patient-specific biokinetics are available, one may improve the accuracy of the absorbed dose estimates, thereby yielding a better approximation to fully patient-specific mean absorbed dose estimates (24,25).

NEW APPLICATIONS OF THE MIRD SCHEMA

Enhancements to the MIRD 5 Revised Anthropomorphic Model

In an effort to improve the accuracy of absorbed dose estimates, several detailed models have been developed for use with the MIRD 5R model. For example, blood and blood vessels have been modeled (32,33), as well as the peritoneal cavity (34), gastrointestinal tract (35,36) and heart (37). In addition, a series of models has been developed, including newborns; 1, 5, 10 and 15 yr olds; and adult man (38). These represent attempts to build more realistic anatomic details into the model, on the not unreasonable assumption that the calculated dose is then a better guide to absorbed dose in the modeled organs.

Two additional enhancements to the MIRD 5R model are found in issues of *The Journal of Nuclear Medicine* appearing in the coming months, namely, MIRD Pamphlet No. 14 Revised, which describes a dynamic bladder model (3), and MIRD Pamphlet No. 15, which details a new dosimetric model for the head and brain (4). The dynamic bladder model replaces the constant-volume model in MIRD 5R. In MIRD 5R, the bladder was represented by an ellipsoid of constant volume 45.73 cm³ containing 202.6 cm³ of urine (23). Changes in size during the filling and emptying of the bladder were ignored which could lead to changes in Φ by as much as an order of magnitude (23). The new dynamic bladder model consists of a spherical source with variable volume to simulate the bladder contents and a wall represented by a spherical shell of constant volume. The model provides for variable urine entry rate, initial bladder contents volume, residual volume and first void time. The voiding schedule includes an extended nighttime gap during which the urine entry rate is reduced to half of the daytime rate. Thus, the dynamic bladder model offers a marked improvement in estimation of the absorbed dose to the bladder wall. It also serves as a tool to study the impact of various parameters on the absorbed dose estimate, thereby providing guidance for establishing dose reduction protocols.

With the advent of highly specific brain imaging agents (39,40), a more detailed dosimetric model of the head and brain is required. The former head and brain model described in MIRD Pamphlet No. 5 (28) treated the brain as a single ellipsoid of soft tissue. The head and neck regions were represented as a truncated elliptical cylinder enclosing the skull, the brain, the spine and the thyroid. The new head and brain model described in MIRD Pamphlet No. 15, which will appear in a future this issue of *The Journal of Nuclear Medicine* (4), attempts to represent more accurately the various structures within the head and brain. Accordingly, the new brain model has eight subregions, including the caudate nucleus, cerebellum, cerebral cortex, lateral ventricles, lentiform nucleus, thalamus, third ventricle and white matter. The brain model is placed within a new head model that includes the neck, cranium, cerebrospinal fluid in cranial region, upper face region, eyes, teeth, mandible, spinal region, thyroid and skin. Absorbed fractions for photon and electron sources located in 13 source regions within this new head and brain model are calculated and used to generate S values for numerous radionuclides used in brain imaging. These S values make it possible to rapidly estimate the absorbed dose to any of the compartments in the new model provided that quantitative data are available on the temporal dependence of activity in the source regions of interest. Techniques for acquiring such data are outlined in MIRD Pamphlet No. 16 published in the February issue of *The Journal of Nuclear Medicine* (5).

Nonuniform Activity Distributions

Although the use of simple models to represent the human body is adequate for many purposes, the mean organ or tumor absorbed dose alone may not always correlate reliably with the biologic response. For instance, much attention has been devoted to the potential biologic implications of nonuniform activity distributions at the macroscopic (41–44), multicellular (45–47) and cellular (48–50) levels in both organs and tumors. However, as pointed out earlier in this article and in other MIRDC Committee publications (20,51), the MIRDC schema is not limited to organ dosimetry. In fact, the MIRDC schema can accommodate complex dosimetric problems, provided that model geometries are developed to represent the biologic system, appropriate S values are calculated and biokinetics data are available at the desired level of detail.

In this issue of *The Journal of Nuclear Medicine*, the MIRDC Committee has provided an additional set of new tools for calculating nonuniform dose distributions over spatial dimensions relevant to clinical nuclear medicine (44,52) and macroscopic autoradiography (47,53–56). These tools take the form of voxel S values, as described in MIRDC Pamphlet No. 17 (6). A voxel S value is the mean absorbed dose to a specified target voxel per unit cumulated activity in a specified source voxel. Thus, the absorbed dose rate to any given target voxel can be obtained by simply summing the contributions from all source voxels, each contribution calculated using the appropriate voxel S value and source voxel activity quantitated as will be discussed in MIRDC Pamphlet No. 16 (5). The tables and figures provided in MIRDC Pamphlet No. 17 offer a convenient and rapid method of calculating three-dimensional dose profiles and dose-volume histograms from quantitative SPECT, PET or autoradiographic images. Such dose profiles and dose-volume histograms may improve the accuracy of predictions of biologic effects of internal radionuclides.

In addition to the voxel S values, the MIRDC Committee recently published a monograph on cellular dosimetry (57). This monograph provides the tools required to calculate the absorbed dose to cells containing radioactivity distributed in the cell nucleus, cytoplasm or on the cell surface. Cellular S values are tabulated for a wide range of cell dimensions for more than 250 radionuclides. Several examples are provided in the monograph to demonstrate the ease with which one can use these S values to estimate cellular absorbed doses.

ABSORBED DOSE AND BIOLOGIC EFFECTS

Although the various approaches discussed in this article for organ, suborgan, multicellular and cellular dosimetry do not constitute an exhaustive list of the possibilities, they do demonstrate the flexibility of the MIRDC Schema for calculating absorbed doses from incorporated radionuclides. However, the absorbed dose alone is sometimes of limited utility in terms of predicting biologic outcome, whether calculated at the organ or cellular level. Other quantities such as radiation quality, subcellular distribution, radiosensitivity, dose rate, repair, repopulation and so on must be considered (58–60). For example, radionuclides that emit radiations of high linear energy transfer, such as alpha particles, require that the RBE of the radiations be considered when predicting the biologic effect of a given radiation absorbed dose (61,62). Although alpha-particle emitters are not widely used in nuclear medicine, Auger electron emitters are used extensively in the clinic (e.g., ^{67}Ga , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{123}I and ^{201}Tl). In vivo and in vitro studies have shown that the RBE of this class of radionuclides varies from as low as unity when the emitter is localized in the cytoplasm to values comparable to that of alpha particles when the emitter is

covalently bound to DNA (63). Therefore, RBE corrections are essential when using absorbed dose to predict the biologic effects of both Auger electron and alpha-particle emitters (64,65).

Although radionuclides that emit low-LET radiations such as photons and beta-particles do not require RBE corrections based on radiation type, dose rate plays a significant role in determining the biologic effects of these radionuclides on biologic systems. The effect of dose rate on the RBE of low-LET radiations has been widely studied (58,66). While the effects can be marked when comparing acute and chronic irradiation conditions, smaller differences are expected when making comparisons between effects caused by chronic irradiation by different radionuclides.

Animal and cell culture models are useful tools with which to explore the consequences of the many variables that affect the biologic consequence of irradiations from internal radionuclides. Animal xenograft and tumor-cell spheroid models have shown that tumors that are most likely to respond to radionuclide targeted therapy are those that are most radiosensitive, have a poor capacity to repair radiation damage, are most sensitive to G_2 blockage and reoxygenate (67,68). The limits of applicability of animal irradiation experiments to the clinical setting in terms of partial volume effects (dose nonuniformity), tumor volume doubling times and host defense mechanisms have been noted (55,69). However, animal models can be used to estimate a ratio of radiobiologic response between radionuclide therapy and external beam therapy or between two different radionuclide therapies. Given knowledge of the ratio of the animal responses, and the clinical response to one of the two therapies from which the ratio was derived, one may project clinical outcome for the new therapy. The biologic effects of diagnostic radiopharmaceuticals can be similarly projected (70).

Nuclear medicine therapy relies on model-based calculations to predict patient response. It should be noted that external-beam radiation therapy also uses model-based calculations; however, the uncertainty in absorbed dose estimates for external-beam treatment-planning calculations are smaller (only 2%–5%) and there is a strong correlation between calculated absorbed dose and response of both tumor and normal tissue. Consequently, one prescribes external beam treatments in units of absorbed dose. For radionuclide therapy, however, treatment is usually prescribed in units of administered activity. This includes therapies for the thyroid (71,72), metastatic bone pain (73) and polycythemia vera (74–76), as well as experimental treatments such as radioimmunotherapy (77). Although correlation of model-based absorbed-dose estimates and biologic response of the tumor tissue is reasonably good for ^{131}I treatment of thyroid carcinoma (78), this is less so for other radionuclide therapies. In addition, clinical results for radioimmunotherapy (24,25,31,79) show that there is only a moderate correlation between model-based absorbed dose calculations and normal tissue response. Nonetheless, this moderate correlation has enabled some radioimmunotherapy clinical trials to prescribe treatment based on maximum tolerated normal-tissue absorbed dose (24,79). The capacity to achieve only moderate correlations is likely due to inadequacies in the models that represent the patient, difficulties in accurately quantitating activity in the relevant organs, nonuniform distribution of radioactivity in the organs, individual differences in radiosensitivity, differences in prior treatment history (e.g., chemotherapy) and other stochastic variables. Clearly, model-based absorbed dose calculations for radionuclide therapy are far more complex and less patient-specific than they are for external

beam therapy. Consequently, investigators are refining their dosimetry models to be more patient-specific (24,79). Individualized patient dosimetry represents a systematic effort to incorporate variations into the model that closely mirror the actual patient. These include anatomic configurations as well as biologic parameters such as the patient's medical condition (e.g., prior treatment history and bone marrow reserve) (24,25,79). These factors and patient-specific three-dimensional dose distributions and dose-volume histograms (6,43,44,80,81) are expected to improve the correlation of dose and response for both tumor and normal tissues.

SUMMARY

The MIRD schema is a general approach for medical internal radiation dosimetry. Although the schema has traditionally been used for organ dosimetry, it is also applicable to dosimetry at the suborgan, voxel, multicellular and cellular levels. The MIRD pamphlets that follow in this issue and in coming issues, as well as the recent monograph on cellular dosimetry, demonstrate the flexibility of this approach. Furthermore, these pamphlets provide new tools for radionuclide dosimetry applications, including the dynamic bladder model, S values for small structures within the brain (i.e., suborgan dosimetry), voxel S values for constructing three-dimensional dose distributions and dose-volume histograms and techniques for acquiring quantitative distribution and pharmacokinetic data.

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