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REVIEW

Nuclear medicine dosimetry

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Abstract

A brief overview is provided of the history of the development of internal dose methods for use in nuclear medicine. Basic methods of internal dosimetry and the systems that have been developed for use in nuclear medicine are described. The development of the MIRD system and the International Radiopharmaceutical Dosimetry Symposium series is outlined. The evolution of models and tools for calculating dose estimates is reviewed. Current efforts in developing more patient-specific methods, particularly for use in therapy calculations, development of small scale and microdosimetry techniques, and of relating internal radiation doses to observed biological effects are described and evaluated.

Some history

It is interesting to trace the history of nuclear medicine dosimetry from the period 1956–2006, as two important defining events fall almost right at the beginning of this period. The first is the development of the technetium-99m generator in 1957 by W D Tucker and colleagues at the Brookhaven National Laboratory. The ability to distribute short-lived radionuclides to sites distant from their point of production, and the unique imaging characteristics of ^{99m}Tc, revolutionized nuclear medicine forever. One of the attractive aspects of all ^{99m}Tc compounds is the delivery of relatively low doses of radiation while producing high-quality diagnostic scans. The second event is the development of the first comprehensive mathematical treatments of radiation dose calculations, by Edith Quimby and Leonidas Marinelli. Two publications by these authors were published in 1948 and 1963. Interesting perhaps only to persons overly fascinated with mathematics, the arithmetic and geometric mean of these years is 1955, so these three defining events perfectly bracket the year 1956!

The investigations of Wilhelm Conrad Roentgen (1845–1923) led to the characterization in 1895 of the penetrating radiation, named 'x rays' (because of their then mysterious nature), which had an enormous and immediate impact on the fields of physics and medicine. The subsequent serendipitous discovery of radioactivity in 1896 by Antoine Henri Becquerel (1852–1908) led to applications of radioactive materials in many industries, not the least of which is medicine. The first discoveries and analyses of potentially useful radioactive

substances, most notably radium and polonium, were made by Pierre Curie (1859–1906) and Marie Curie (1867–1934). In 1901, Henri Alexandre Danlos and Eugene Bloch first used radioactive sources (radium) in direct contact with tuberculous skin lesions for therapy involving radioactive materials. Then Frederick Proescher published in 1913 the first recorded study on the systemic application of radium in the therapy of a number of diseases. The use of radiotracers dates to 1924, when Georg de Hevesy and colleagues studied the movements of lead-210 and bismuth-210 in animals. Herrman Blumgart and Otto Yens later (1925) used bismuth-214 to study blood flow rates in human subjects. Two radionuclides of high importance to medical applications, iodine-131 and cobalt-60, were discovered by John Livingood and Glenn Seaborg, while Emilio Segre and Glenn Seaborg discovered technetium-99m in 1938. Iodine-131 and technetium-99m continue to be the predominate radionuclides used in diagnostic and therapeutic nuclear medicine studies. In 1946, Allen Reid and Albert Keston then discovered the iodine isotope iodine-125, which played a significant role in radioimmunoassay studies, as well as in general nuclear medicine. In 1948, the first commercial distribution of radionuclides was begun by Abbott Laboratories, with the first distribution of iodine-131 as a radiopharmaceutical in 1950. Iodine-131 as sodium iodide became the first U.S. Food and Drug Administration (FDA) approved radiopharmaceutical in 1951. In 1953, Gordon Brownell and H H Sweet built a positron detector based on the detection of annihilation photons by means of coincidence counting. It was not until 1999, however, that positron emitting radiopharmaceuticals would come into routine clinical use, as the U.S. Health Care Finance Administration (HCFA) finally moved to approve reimbursement (Medicare and Medicaid covered patients) of positron emission tomography (PET) scans for the diagnosis and staging of many cancers. Subsequently, the use of PET radiopharmaceuticals has skyrocketed. It was in 1958 that Hal Anger invented the 'scintillation camera' (also often called an 'Anger camera'), the imaging device that permits complex two- and three-dimensional imaging of the distribution and kinetics of radiopharmaceuticals in the body. The main day-to-day use is simply for creating medical images of subjects for diagnosis, but radiation dose calculations based on human image data come almost exclusively from data gathered with gamma cameras in some way or another.

Radiation dose calculations

To estimate absorbed dose for all significant tissues, one must determine for each tissue the quantity of energy absorbed per unit mass. This yields the quantity absorbed dose, if expressed in proper units, and can be extended to calculation of dose equivalent if desired. We will derive the quantities needed to calculate the two key parameters (energy and mass) via study of an object that is assumed to be uniformly contaminated with radioactive material. Depending on the identity of the radionuclide, particles or rays of characteristic energy and abundance will be given off at a rate dependent on the amount of activity present. The object has some mass. Most of the quantities needed for a calculation of dose are now defined: the energy per decay (and number per decay), activity and mass of the target region. One other factor needed is the *fraction of emitted energy* that is absorbed within the target. This quantity is most often called the absorbed fraction and is represented by the symbol ϕ. For photons (gamma rays and x rays) some of the emitted energy will escape objects of the size and composition of interest to internal dosimetry (mostly soft tissue organs with diameters of the order of centimetres). For electrons and beta particles, most energy is usually considered to be absorbed, so we usually set the absorbed fraction to 1.0. Electrons, beta particles and the like are usually grouped into a class of radiations referred to as 'nonpenetrating' emissions, while x and gamma rays are

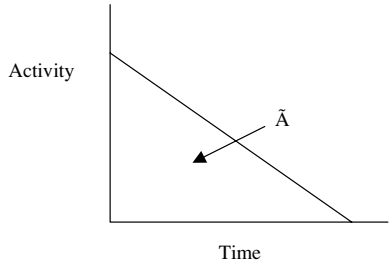
called 'penetrating' radiations. We can now show a generic equation for the absorbed dose rate in our object as

$$\dot{D} = \frac{k\,A \sum_i n_i E_i \phi_i}{m}, \tag{1}$$

where $\dot{D}$ is the absorbed dose rate (rad h^{-1} or Gy s^{-1}), A is the activity (μCi or MBq), n is the number of radiations with energy E emitted per nuclear transition, E is the energy per radiation (MeV), ϕ is the fraction of energy emitted that is absorbed in the target, m is the mass of target region (g or kg) and k is the proportionality constant (rad g μCi^{-1} h^{-1} MeV^{-1} or Gy kg MBq^{-1} s^{-1} MeV^{-1}).

It is extremely important that the proportionality constant be properly calculated and applied. The results of our calculation will be useless unless the units within are consistent and they correctly express the quantity desired. The application of *radiation weighting factors* (once called 'quality factors') to this equation to calculate the dose equivalent rate is a trivial matter; for most of this review, we will consider only absorbed doses for discussion purposes.

The investigator is not usually interested only in the absorbed dose rate; more likely, an estimate of total absorbed dose from an administration is desired. In equation (1), the quantity activity (nuclear transitions per unit time) causes the outcome of the equation to have time dependence. To calculate cumulative dose, the time integral of the dose equation must be calculated. In most cases, the only term which has time dependence is activity, so the integral is just the product of all of the factors in the above equation except for activity by the integral of the time–activity curve.



Regardless of the shape of the time–activity curve, its integral, however obtained, *will have units of the number of total nuclear transitions* (activity, which is transitions per unit time, multiplied by time). Therefore, the equation for cumulative dose would be shown as

$$D = \frac{k\tilde{A} \sum_i n_i E_i \phi_i}{m}, \tag{2}$$

where D is the absorbed dose (rad or Gy) and $\tilde{A}$ is the cumulated activity (μCi h or MBq s).

Dosimetry systems

The above equations are generic cumulative dose equations. Many authors have developed this equation in one form or another to apply to different situations. Usually many of the factors in the equations are grouped together to simplify calculations, particularly for radionuclides with complex emission spectra. Some of the physical quantities such as absorbed fraction and mass can also be combined into single values. However, these quantities may be grouped, hidden or otherwise moved around in different systems; all of them incorporate the concepts from these equations, and all are based on the same principles. Given the same input data and assumptions, the same results will be obtained. Sometimes, the apparent differences between

the systems and their complicated-appearing equations may confuse and intimidate the user who may be frustrated in trying to make any two of them agree for a given problem. Careful investigation to discern these grouped factors can help to resolve apparent differences.

Marinelli/Quimby method

Publications by Marinelli *et al* (1948) and Quimby and Feitelberg (1963) gave the dose from a beta emitter that decays completely in a tissue as

$$D_\beta = 73.8 C E_\beta T, \tag{3}$$

where D_β is the dose in rad, C is the concentration of the nuclide in microcuries per gram, E_β is the mean energy emitted per decay of the nuclide and T is the half-life of the nuclide in the tissue. As will be shown later, the cumulated activity is given as 1.443 times the half-life times the initial activity in the tissue. The other terms in equation (3) are as follows: $k = (73.8/1.443) = 51.1$, C is activity per mass, and for beta emitters, we assume that ϕ is 1.0. The factor 1.443 is $(1/\ln(2))$, a factor which occurs during the integration of the $e^{-\lambda t}$ term in the term for radioactivity removal. For gamma emitters, values of ϕ were estimated from the geometrical factors of Hine and Brownell (1956) for spheres and cylinders of fixed sizes. Dose rates were based on expressions for dose near a point-source gamma emitter integrated over the source volume:

$$D_\gamma = 10^{-3} \Gamma C \int_v \frac{e^{-\mu r}}{r^2}\, dV \qquad (\text{rad h}^{-1}). \tag{4}$$

It is difficult to see how this equation fits the form of our general equation, but it does. The factor C is the activity per unit mass. The specific gamma rate constant Γ essentially gives the exposure rate per disintegration into an infinite medium from a point source (equivalent to $k \times \sum n_i \times E_i$ in the generic equation). Finally, the factor $\left[\int \exp(-\mu r)/r^2\, dV\right]$ acts like an absorbed fraction (μ is an absorption coefficient and $1/r^2$ is essentially a geometrical absorbed fraction). The integral in this expression can be obtained analytically only for simple geometries. Solutions for several standard objects (spheres, cylinders and so forth) were provided in the geometrical factors in Hine and Brownell's text.

MIRD system

While Marinelli and Quimby defined the first dosimetry system, the system that defined medical internal dosimetry for many years is the system developed by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine. The well-known physician and one-time member of the MIRD Committee Dr Carol Marcus related to me a charming story of an encounter with Edith Quimby:

> Shortly after I began teaching Radioisotope Methodology and Radiation Biology in the Radiopharmacy Program at USC, I was sent by the Director, Walter Wolf, to Oak Ridge for the Dec. 8–11, 1969 symposium entitled, 'Medical Radionuclides: Radiation Dose and Effects'. The real reason Walter sent me was that he wanted me to get to know the leaders in nuclear medicine and set up an internship program for our M.S. in Radiopharmacy graduates beginning June, 1970. The meeting was overwhelmingly male-dominated. There were only 5–6 female participants, including me, Cecilia Motta-Otero (one of my graduate students), Evelyn Watson, Edythalena Tompkins, and Edith Quimby. There was only one ladies' room, and I found myself washing my hands at the next sink from Edith Quimby. What would a

Table 1. Selected MIRD pamphlets.

Pamphlet	Publication date	Main information
1, 1 revised	1968, 1976	Discussion of MIRD internal dose technique
3	1968	Photon absorbed fractions for small objects
5, 5 revised	1969, 1978	Description of anthropomorphic phantom representing Reference Man, photon absorbed fractions for many organs
7	1971	Dose distribution around point sources, electron, beta emitters
8	1971	Photon absorbed fractions for small objects
11	1975	*S*-values for many nuclides
12	1977	Discussion of kinetic models for internal dosimetry
13	1981	Description of model of the heart, photon absorbed fractions
14, 14 revised	1992, 1999	Dynamic urinary bladder for absorbed dose calculations
15	1996	Description of model for the brain, photon absorbed fractions
16	1999	Outline of best practices and methods for collecting and analysing kinetic data
17	1999	*S*-values for voxel sources
18	2001	Administered activity for xenon studies
19	2003	Multipart kidney model with absorbed fractions

young 30-year-old nobody like me say to the Great Quimby? Well, I politely asked her what she thought of this new "MIRD scheme". She paused, looked at me sternly, and said "Young woman, it's terrific! It's much better than my old method, and you *will* learn it!" I thanked her, and said I would, and went right back to the meeting and started taking it seriously. After the meeting, I took the Great Red Pamphlets home and began learning from them.

The 'great red pamphlets' of the MIRD system indeed defined the methods, equations and models for nuclear medicine dosimetry for many years. A listing of selected MIRD pamphlets is given in table 1.

All members of the MIRD Committee over the decades contributed to the fine efforts and publications. Three, however, that were particularly influential were Robert Loevinger, Walter Snyder and Evelyn Watson. Drs Loevinger and Snyder represented much of the genius and driving force that initially defined the equations and models around which the system was organized, and who spearheaded many of the investigations and key publications that defined the system. Evelyn Watson, working with Roger Cloutier in Oak Ridge, also was involved in several key seminal MIRD Publications, and they as well organized an important series of symposia on radiopharmaceutical dosimetry (the first in the series was the one that Dr Marcus attended) (see table 2). The proceedings of these symposia remain as important references on the shelves of anyone working in the field.

Many of the papers in these proceedings provided very important models, methods and data related to radiopharmaceutical dosimetry that are not available elsewhere. Roger Cloutier and Evelyn Watson, with Audrey Schlafke-Stelson, published their own history of medical internal dosimetry in 1995 (Schlafke-Stelson *et al* 1995). This important paper contains numerous insights and individual memories of these authors, who were directly involved in the developmental years of medical internal dosimetry. Roger Cloutier was always a highly sought after speaker, on many subjects, only one of which was radiopharmaceutical dosimetry.

Table 2. The Radiopharmaceutical Dosimetry Symposium series.

Medical Radionuclides: Radiation Dose and Effects Oak Ridge Associated Universities, Oak Ridge, TN 8–11 December 1969 Proceedings: U.S. Atomic Energy Commission, AEC Symposium Series 20, CONF-691212, 1970
Radiopharmaceutical Dosimetry Symposium Oak Ridge Associated Universities, Oak Ridge, TN 26–29 April 1976 Proceedings: U.S. Food and Drug Administration, HEW Publication (FDA) 76-8044, 1976
Third International Radiopharmaceutical Dosimetry Symposium Oak Ridge Associated Universities, Oak Ridge, TN 7–10 October 1980 Proceedings: U.S. Dept of Health and Human Services, HHS Publication FDA 81-8166, 1981
Fourth International Radiopharmaceutical Dosimetry Symposium Oak Ridge Associated Universities, Oak Ridge, TN 5–8 November 1985 Proceedings: Oak Ridge Associated Universities, 1986
Fifth International Radiopharmaceutical Dosimetry Symposium Oak Ridge Associated Universities, Oak Ridge, TN 7–10 May 1991 Proceedings: Oak Ridge Associated Universities, 1992
Sixth International Radiopharmaceutical Dosimetry Symposium Oak Ridge Associated Universities, Oak Ridge, TN 7–10 May 1996 Proceedings: Oak Ridge Associated Universities, 1999
Seventh International Radiopharmaceutical Dosimetry Symposium Vanderbilt University, Nashville, TN 17–19 April 2002 Proceedings: in several issues of Cancer, Biotherapy, and Radiopharmaceuticals, 2003

His command of the technical data was complemented with a lively and provocative speaking style. For example, on the subject of uncertainty in internal dose data, he has been heard to say, "I only use one significant digit in reporting internal dose values because you can't use any fewer!"

The equation for absorbed dose in the MIRD system (Loevinger *et al* 1988) is deceptively simple:

$$D_{r_k} = \sum_h \tilde{A}_h S(r_k \leftarrow r_h). \tag{5}$$

In this equation, r_k represents a target region and r_h represents a source region. The cumulated activity is given in the term $\tilde{A}_h$; all other terms from our basic equation above must be lumped in the factor S, and so they are

$$S(r_k \leftarrow r_h) = \frac{k \sum_i n_i E_i \phi_i (r_k \leftarrow r_h)}{m_{r_k}}. \tag{6}$$

The use of the 'S factor' approach greatly facilitated dose calculations. Boiling the dose calculation down to a two-factor calculation allowed many to perform routine dose calculations, first with a pencil and paper, perhaps using a slide rule (see the paper by Schlafke-Stelson *et al* (1995)), later with a calculator, and eventually using a computer program, as will be discussed shortly.

RADAR

In the early 21st century, an electronic resource was established on the internet to provide rapid, worldwide dissemination of important dose quantities and data. The RAdiation Dose Assessment Resource (RADAR) established a web site at www.doseinfo-radar.com and provided a number of publications on the data and methods used in the system. The RADAR system (Stabin and Siegel 2003) has about the simplest manifestation of the dose equation:

$$D = N \times \mathrm{DF}, \tag{7}$$

where N is the number of disintegrations that occur in a source organ and DF is

$$\mathrm{DF} = \frac{k \sum_i n_i E_i \phi_i}{m}. \tag{8}$$

The DF is mathematically the same as an '*S* value' as defined in the MIRD system. The number of disintegrations is the integral of a time–activity curve for a source region. RADAR members produced compendia of decay data, dose conversion factors and catalogued standardized dose models for radiation workers and nuclear medicine patients, among other resources. They also produced the widely used OLINDA/EXM personal computer software code (Stabin *et al* 2005), which used the equations shown here and the input data from the RADAR site. This code is discussed further below.

International Commission on Radiological Protection

The ICRP has developed two comprehensive internal dosimetry systems intended for use in occupational settings (mainly the nuclear fuel cycle).

The real innovation in the ICRP 30 system is the so-called effective dose equivalent (H_e or EDE). Certain organs or organ systems were assigned dimensionless weighting factors that are a function of their assumed relative radiosensitivity for expressing fatal cancers or genetic defects. The assumed radiosensitivities were derived from the observed rates of expression of these effects in various populations exposed to radiation. Multiplying an organ's dose equivalent by its assigned weighting factor gives a weighted dose equivalent. The sum of weighted dose equivalents for a given exposure to radiation is the effective dose equivalent. It is the dose equivalent that, if received uniformly by the whole body, would result in the same total risk as that actually incurred by a nonuniform irradiation. It is entirely different from the dose equivalent to the whole body that is calculated using values of SEE for the total body. Whole-body doses are often meaningless in internal dose situations because nonuniform and localized energy deposition is averaged over the mass of the whole body (70 kg).

One real difference that exists between doses calculated with the ICRP II system and the ICRP 30 (and MIRD) system is that the authors of ICRP II used a very simplistic phantom to estimate their absorbed fractions. All body organs and the whole body were represented as spheres of uniform composition. Furthermore, organs could only irradiate themselves, not other organs. So, although contributions from all emissions were considered, an organ could only receive a dose if it contained activity, and the absorbed fractions for photons were different from those calculated from the more advanced phantoms used by ICRP 30 and MIRD. As noted above, the ICRP has published important compendia of dose estimates for many standard radiopharmaceuticals (ICRP 1989, 2000). The MIRD Committee published dose estimates for a handful of radiopharmaceuticals in its 'dose estimate reports', but the ICRP publications supersede these publications both in the quantity of pharmaceuticals treated and in the breadth of source data used to support the dose calculations.

Available models for dose factors

Body and organ models

The current generation of anthropomorphic phantoms began with the development of the Fisher–Snyder phantom (Snyder *et al* 1969). This phantom used a combination of geometric shapes—spheres, cylinders, cones, etc—to create a reasonably accurate anatomic representation of the body. This phantom was used with Monte Carlo computer programs which simulated the creation and transport of photons through these various structures in the body, whose atomic composition and density were based on data provided in the ICRP report on Reference Man (ICRP 1975). This report provided various anatomical data assumed to represent the average working adult male in the Western hemisphere. Although this was most directly applicable to use with adult males, the phantom also contained regions representing organs specific to the adult female. Using this phantom, radiation doses were calculated for adults based on activity residing in any organ and irradiating any other organ. Absorbed fractions at discrete photon energies were calculated and published by the MIRD Committee (Snyder *et al* 1978). In addition, dose conversion factors, called S values, as described above, which represented the dose to a target region per nuclear transition in a source region (approximately 20 source and target regions were defined) for over 100 radionuclides, were also published (Snyder *et al* 1975).

The development of the series of phantoms by Cristy and Eckerman (1987) allowed dose calculations for different individuals of different size and age. Six phantoms were developed, which were assumed to represent children and adults of both genders. Absorbed fractions for photons at discrete energies were published for these phantoms, which contained approximately 25 source and target regions. Tables of S values were never published, but ultimately were made available in the MIRDOSE computer software (Stabin 1996). The publication of phantoms for the adult female, both nonpregnant, and at three stages of pregnancy (Stabin *et al* 1995) modelled the changes to the uterus, intestines, bladder and other organs that occur during pregnancy and included specific models for the foetus, foetal soft tissue, foetal skeleton and placenta. S values for these phantoms were also made available through the MIRDOSE software. Others have also proposed more detailed models of some organs and other structures, including the brain (Eckerman *et al* 1981, Bouchet *et al* 1999), eye (Eckerman *et al* 1981, Holman *et al* 1983), peritoneal cavity (Watson *et al* 1989), prostate gland (Stabin 1994), bone (Eckerman and Stabin 2000, Bouchet *et al* 1999), rectum (Mardirossian *et al* 1999, Cross *et al* 1992) and small unit density spheres, possibly to represent tumours, organs in small animals or other structures (Stabin and Konijnenberg 2000). Some of these models were implemented for use in the OLINDA/EXM code (see below).

Bone and marrow models

This area of dose modelling is quite complex and has been the focus of many lengthy investigations over the past half century. The reader is referred to a recent summary on this subject (Stabin *et al* 2002), and all of the history of this particularly difficult area of dosimetry is not reproduced here, merely in the interest of space.

Calculational tools

The MIRDOSE code series began with a Tektronix PC-based MIRDOSE 1 code (Watson and Stabin 1984), then migrated to the MIRDOSE 2 code in the PC-DOS environment, and MIRDOSE 3 and 3.1 in the PC-Windows environment (Stabin 1996). MIRDOSE has been

widely used by the nuclear medicine community and cited in the literature and in presentations at scientific meetings as the basis for presented internal dose estimates. The MIRDOSE 2 and 3 codes implemented the use of whole-body MIRD stylized mathematical phantoms representing adult males and females, children and pregnant women. The codes automated the calculation of internal dose for a large number (>200) of radiopharmaceuticals in these phantoms, the rapid comparison of calculations for different cases, examination of dose contributions to different organs and regional marrow dose calculations. The code was also widely used as a tool for teaching internal dosimetry in universities and professional training centres.

MIRDOSE was basically replaced by a new generation code, named OLINDA/EXM (Organ Level INternal Dose Assessment with EXponential Modelling) (Stabin *et al* 2005), employing the Java programming language and the Java Development Kit environment. The entire code was rewritten, but all of the basic functions of the MIRDOSE code were retained, and others were extended. More individual organ phantoms were included, the number of radionuclides was significantly increased (to over 800, including many alpha emitters), and the ability to perform minor patient-specific adjustments to doses reported for the standard phantoms was made available.

Development of image-based dosimetry approaches

Imaging of patients to obtain anatomical and physiological information has matured greatly in the last decade. Anatomic information obtained with magnetic resonance imaging (MRI) or computed tomography (CT) is usually expressed in three dimensions (3D) in voxel format, with typical resolutions on the order of 1 mm. Similarly, SPECT and PET imaging systems can provide 3D representation of activity distributions within patients, also in voxel format, with typical resolutions of around 5–10 mm. The newest systems now combine CT with both PET and SPECT state-of-the-art imaging systems on the same imaging gantry, so that patient anatomy and tracer distribution can be imaged during a single imaging session without the need to move the patient, thus greatly improving and facilitating image registration. The use of a well-supported radiation transport code such as MCNP or EGS4 with knowledge of patient anatomy will result in a significant improvement in the accuracy of dose calculations. Radiation dose calculations for nuclear medicine applications have been mostly relegated to abstract and theoretical calculations, used to establish dosimetry for new agents and provide reasonable dose estimates to support radiopharmaceutical package inserts and for use in open literature publications. When patients are treated in therapy with radiopharmaceuticals, careful, patient-specific optimization is not performed, as is routine in radiation therapy with external sources of radiation (radiation producing machines, brachytherapy). There are several reasons for this. One involves the limitations on spatial resolution and accuracy of activity quantification with nuclear medicine cameras. Another has to do with the realism and specificity to an individual patient of available body models. The models described above were designed to represent the ‘reference’ adult male and female, children and so on. Besides using geometric primitives to represent the body and its various organs, only one model is available for any category of individual, so dose estimates calculated using this approach will contain significant uncertainties when applied to any subject, and physicians understandably have low confidence in the use of these results to plan individual subject therapy. Thus, unfortunately for the patients, a ‘one dose fits all’ approach to therapy is usually employed, with significant caution resulting in administration of lower than optimum levels of activity to the majority of subjects. The use of image-based models, not only to develop new ‘reference’ phantoms, but also to permit the use of patient-specific models for each therapy patient, is now well developed. Internal dosimetry is thus poised to truly enter into a ‘Golden Age’ in which it will become a

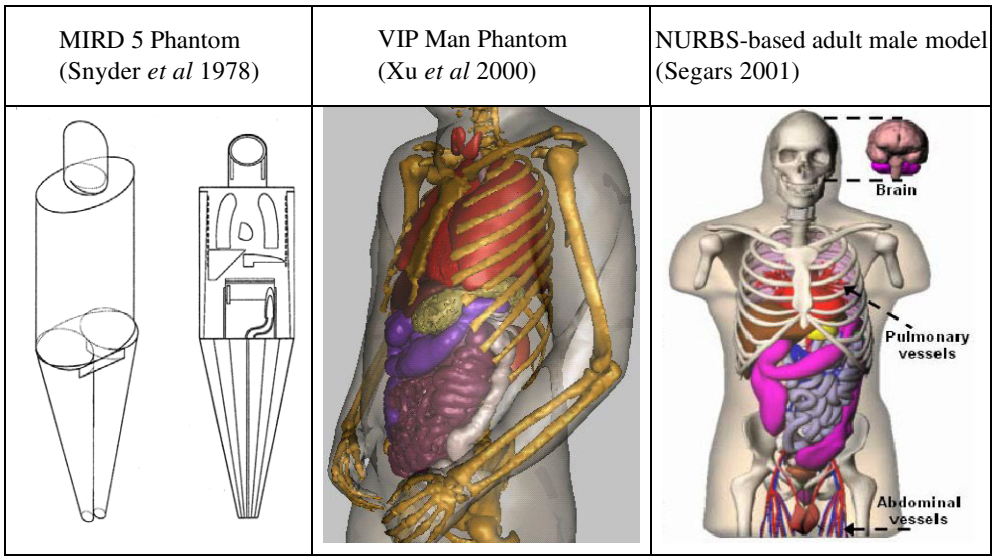


Figure 1. Comparison of the realism of the traditional MIRD body models with those being used to support current dose modelling efforts.

(This figure is in colour only in the electronic version)

more integral part of cancer patient care, as dosimetry is used in external source radiotherapy. The realism of the newer models is shown in figure 1, with comparison to the form of the existing models developed and implemented in the historical MIRD system.

Image-based computational tools

Several of the efforts to use image data to perform dose calculations, as described above, include the 3D-ID code from the Memorial Sloan-Kettering Cancer Center (Kolbert *et al* 1997), the SIMDOS code from the University of Lund (Dewaraja *et al* 2005), the RTDS code at the City of Hope Medical Center (Liu *et al* 1999) and the DOSE3D code (Clairand *et al* 1999). The code with the most clinical experience to date is the 3D-ID code. These codes rely on either the standard geometrical phantoms (MABDose and DOSE3D) or patient-specific voxel phantom data (3DID and SIMDOS) and various in-house written routines to perform photon transport. Neither has a particularly robust and well-supported electron transport code, such as is available in EGS (Bielajew and Rogers 1987) or MCNP (Briesmeister 2000). The PEREGRINE code (Lehmann *et al* 2005) has also been proposed for three-dimensional, computational dosimetry and treatment planning in radioimmunotherapy.

The usual approach used in these codes is to assume that electron energy is absorbed wherever the electron is first produced. The development and support of electron transport methods is quite complex, as evidenced by ongoing intensive efforts by both the EGS4 and MCNP computer code working groups. It is not reasonable to expect in-house written codes to deal effectively with electron transport. In areas of highly nonuniform activity distribution, such as an organ with multiple tumours evidencing enhanced uptake of an antibody, explicit transport of both photons and electrons is needed to characterize dose distributions adequately.

Investigators at Vanderbilt University have demonstrated the capability for performing radiation transport in voxel phantoms with the MCNP Monte Carlo radiation transport code for

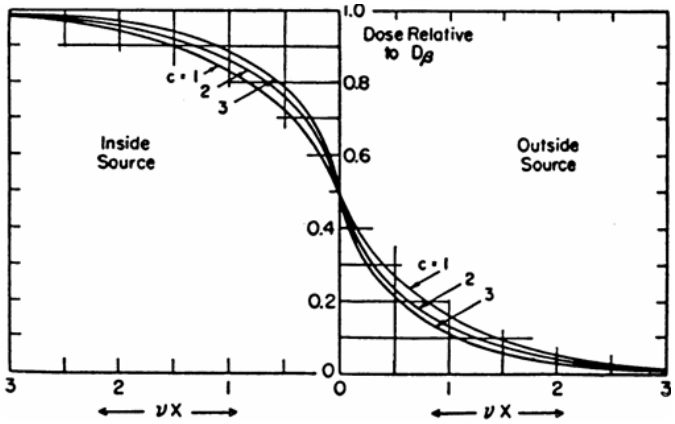


Figure 2. Dose distribution inside (left) and outside (right) the surface of an infinite plane source of a β emitter, from Loevinger *et al* (1956).

internal sources (Yoriyaz *et al* 2001, Stabin and Yoriyaz 2002) in the voxel phantom provided by the group at Yale (Zubal *et al* 1994), while investigators at Rensselaer Polytechnic Institute have demonstrated the capability using the EGS code for external sources (Chao *et al* 2001, Xu *et al* 2000) in the VIP man voxel phantom (Xu *et al* 2000). Jones (1998) reported work performed at the NRPB, UK on an adult male model called NORMAN using MR images of 2 mm $\times$ 2 mm resolution and 10 mm slice thickness. Their model was used to estimate organ doses from external photon sources over a range of energies and irradiation geometries. When comparing their calculations to those which used a MIRD-type stylized model, differences in organ doses were found to range from a few per cent to over 100% at photon energies between 10 and 100 keV. Petoussi-Henss *et al* (2002) reported a family of tomographic models developed from CT images of 2 mm $\times$ 2 mm resolution and 8 mm slice thickness. Dose coefficients from external irradiation with these phantoms were substantially different than values derived using the MIRD phantom, suggesting to these authors that the MIRD models do not represent well a large proportion of the population.

Small scale and microdosimetry

There is a perception that standard MIRD methods and models are only useful for whole-organ or whole-body dosimetry. It is true that most of the published model results for nuclear medicine applications in the MIRD system have dealt with doses that are averaged over whole organs. In the past 15–20 years, there has been considerable interest in performing more detailed dosimetry calculations at the tissue and cellular level. The perception that the MIRD technique is not adequate for such calculations is clearly incorrect. Some of the earliest publications in the MIRD literature and the internal dosimetry symposia dealt with dose distributions within tissues (sometimes called 'small scale' dosimetry). The science of microdosimetry, which involves stochastic representations of dose distributions usually at a cellular level, has been under development since the 1960s, being first formally treated by Rossi in various publications (e.g. Rossi (1968)). Calculating absorbed dose as a function of distance from point or extended photon or electron-emitting sources has been facilitated for many years by the formulae of Loevinger *et al* (1956) and the point kernels of Berger (1971a). In the first international dosimetry symposium, Berger (1971b) showed how to extend his results to line, plane and volume sources. Figure 2 from Loevinger *et al* (1956) shows the

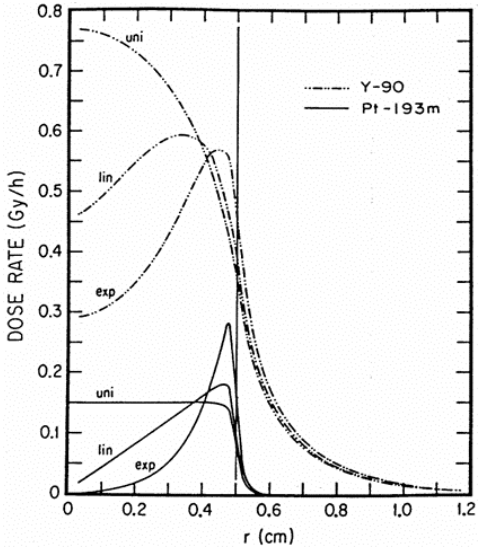


Figure 3. Dose rate profile for ^{90}Y and ^{193m}Pt in a tumour of 0.5 cm radius, with three different assumed activity distributions (uniform, linear and exponential), from Howell *et al* (1989).

calculated dose distribution outside and inside an infinite plane source of infinite thickness containing a β source. The distances near the source are given in terms of νx, the product of the observed 'absorption coefficient' and true distance x. The doses are given as a fraction of D_β, which is the 'infinite medium dose', or the dose throughout the slab away from the edge (this is the dose that we usually calculate in the MIRD system when we define the average dose to a region).

Other efforts, for example by Cross *et al* (1992), Werner *et al* (1991) and Howell *et al* (1989), have yielded useful information for therapy treatment planning with certain short-ranged emitters. Howell *et al* used Cole's formulae (Cole 1969) for electron energy loss (which also employ CSDA approximations). In figure 3, Howell *et al* show dose rate profiles for Y-90 and Pt-193m assumed to be distributed throughout a spherical tumour of 0.5 cm radius with three different patterns (uniformly distributed, and linearly and exponentially distributed).

The use of point kernels and analytical methods are not as common currently as characterization of dose distributions using Monte Carlo codes such as MCNP (Briesmeister 2000) or EGS (Bielajew and Rogers 1987). For example, Stabin *et al* (2000) estimated dose distributions around hypothetical intravascular brachytherapy sources using MCNP.

The use of alpha or short-range electron emitters in radioimmunotherapy has brought microdosimetry into a practical role in medical dosimetry. Reviews by Stinchcomb and Roeske (1992) and Humm *et al* (1993) have outlined microdosimetric concepts and methods and provided some sample calculations illustrating its application to specific labelled compounds. Figure 4 shows an example from Humm *et al* in which the dose distribution to tumour cell nuclei from ^{211}At and its progeny ^{211}Po is plotted.

Relating calculated radiation dose to effect

The goal of all forms of radiation therapy against cancer is to give lethal doses of ionizing radiation to malignant cells while not exceeding the radiation tolerance of involved normal

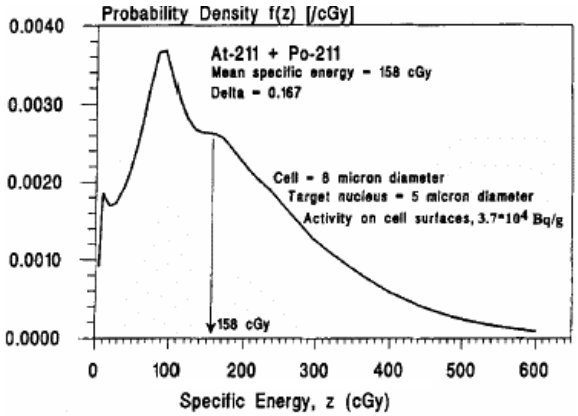


Figure 4. Dose distribution to tumour cell nuclei from ^{211}At and its progeny ^{211}Po, from Humm *et al* (1993).

tissues. The last frontier, which is as of yet largely unexplored, that must be traversed before internal dose estimates will have a similar significance and utility to individual treatment planning as does dosimetry with external sources of radiation is that of relating calculated dose from internal emitters to observed biological effects. Understanding of the tolerances of normal tissues to radiation from external sources has grown over the years since radiation therapy has become routine, from experience with many patients and sharing of data. New radiolabelled agents under investigation for possible use in treatment of cancer are evaluated in clinical trials in which safety and efficacy are studied carefully. The relationship between results from internal and external sources of radiation was reviewed recently by Stabin and Brill (2006). A recent overview article by Meredith (2002) summarizes current knowledge in this area. In her paper, Dr Meredith points out several problems with the interpretation of these data, namely that (1) the internal dose data are generally not as accurate as external dose data, as they do not as carefully account for lack of radionuclide homogeneity within the tissues, tissue density changes which may have affected the image quantification and other factors, (2) tracer studies used to establish the biokinetics (and thus the dosimetry) may have different biokinetic patterns than when the full therapeutic dose is given, as has been documented in several studies, and (3) lack of uniformity of reporting of internal dose results, depending on which image quantification methods, computer programs, dose conversion factors, etc were used. Interpretation of the findings is difficult due to the complexities in the format of the reported results as well. Nonetheless, the data may suggest that a higher tolerance has been observed for internally administered radionuclides, implying that the low dose rate effects cause a lower tissue response given the same level of absorbed dose (Gy). It is also, however, reasonable to expect that this effect will vary considerably with differences in radiopharmaceutical effective half-time in the tissue. Short-lived agents will deliver their dose in a shorter time, thus more approximating the dose rates of external beam radiation, while longer lived agents, whose dose is delivered over many days to weeks, will deliver the dose to the tissues at a considerably lower dose rate especially at later times.

There is also high interest in verifying calculated internal doses by direct measurement. Thermoluminescent (TLD) devices have a wide relatively flat response independent of energy and a wide linear sensitivity to dose. These have been used mostly in inanimate phantoms, but have been used in animal studies, and have been proposed for some human applications. These are integrating devices and read out the dose absorbed between the time implanted and the

time when retrieved from the subject. Small thermoluminescent dosimeters (TLDs) have been very useful in anthropomorphic phantoms in calibration of diagnostic and therapeutic external radiation sources, and attempts were made to place them into small animals, principally in tumours to measure accumulated radiation doses over time (Demidecki *et al* 1993, Yorke *et al* 1993). Calibration of the *in vivo* TLDs and interpretation of the data, however, proved problematic, most likely due in part to interactions of the dosimeter material with tissues. Glass-encapsulated MOSFET detectors have been successfully used for radiation dosimetry with IMRT and RIT (Gladstone *et al* 1994, Gladstone and Chin 1995) and are under continued development. These devices show potential for use with high-energy beta monitoring (such as with ^{90}Y), but have difficulties due to attenuation in the glass wall of the device. Nonetheless, they may be of value in the validation of absorbed dose estimates from external beam and from internal emitter therapy, such as with ^{90}Y spheres currently being used in nuclear medicine therapy.

Summary

The calculation of dose from internal emitters has come a long way since its inception in 1948 and 1963 by Marinelli and Quimby. The first major revolution occurred in the 1970s with the development of the MIRD models and calculational techniques. These methods, however, have proven to be inadequate for the calculation of doses sufficiently detailed and accurate to plan individual patient therapy, as is routinely done with external radiation sources. The second major revolution is now underway, involving the use of realistic and patient-specific body models based on medical image data. This permits the calculation of highly detailed, 3D dose distributions, dose volume histograms and other data. The last revolution that is needed to truly push internal dosimetry into a Golden Age is the linking of such high-quality radiation dose estimates to biological effects, which is only now being explored with much fervor.

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Biography

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