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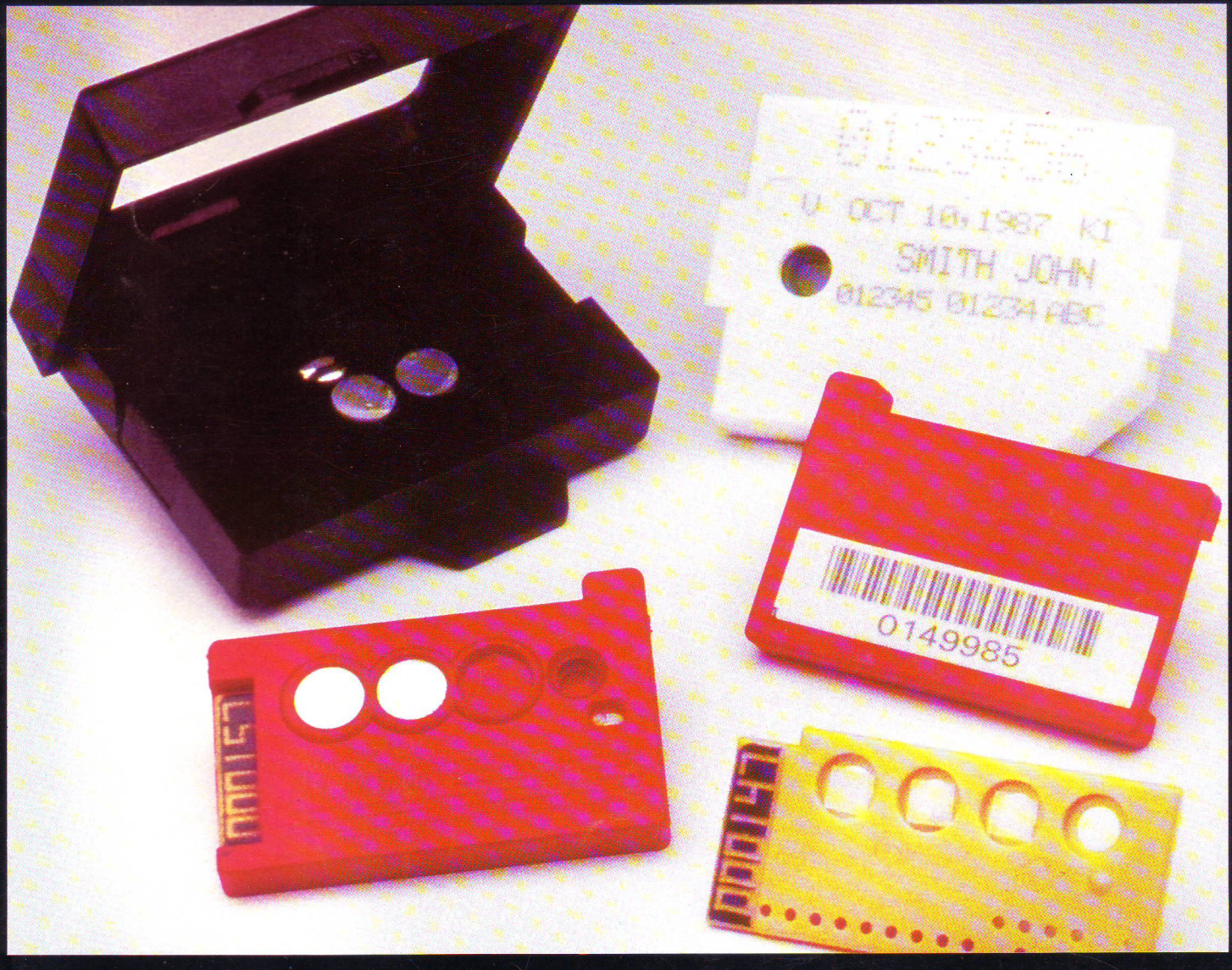

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Internal Doslmetry in Nuclear Medicine: A Summary of its Development, Applications and Current Limitations

by M. Lyra and P. Phinou

Introduction

In this article, a historical presentation of the development of internal dosimetry is combined with a summary of its applications in the field of nuclear medicine. Internal absorbed dose estimates are essential for the implementation of the ALARA principle in routine clinical practice and the risk evaluation associated with radionuclide administration, especially for therapeutic purposes. Basic concepts of calculating the age-dependent mean tissue dose and the distribution of the local tissue dose are presented together with modeling techniques based on biokinetics. In addition, computerized approaches to absorbed dose calculations in a target region from a source region are reported. Most of them rely on a standard "reference man" geometry and assume a uniform distribution of radionuclides. Several modifying approaches to further increase the accuracy of calculations are summarized.

Major limitations in absorbed dose calculations are presented and discussed. These limitations result from the difficulty inherent in measuring radioactivity inside the body, as well as from the use of standard generalized biokinetic models which, in reality, vary considerably in each patient. Possible underestimation of risks by the currently adopted dosimetric procedures, especially in the case of radionuclides decaying by electron capture and internal conversion, is discussed. Finally, special considerations are summarized regarding applications that demand an accurate estimate of absorbed dose such as the use of radionuclides for therapy purposes.

Historical Review

Internal dosimetry began soon after the development of charged particle accelerators in the mid 1930s, which made it possible to produce and use several radionuclides for diagnostic and therapeutic purposes. Radium, discovered by Marie Curie in 1898, was the first radionuclide to be used, both for therapy (small capsules and needles containing the radioisotope) and in tracer studies, being the first radioisotope with specific activity high enough to make tracer studies possible.[11]

The first tracer study in humans—to measure blood flow using radon[2]—was performed in the late 1920s by Hermann L. Blumgart et al. During the 1930s, the discovery of artificial radioactivity by Frederick Joliot and his wife Irene Joliot-Curie (1934) and the development of charged particle accelerators provided a variety of artificially made isotopes. These isotopes could be introduced into the body for tracing or therapeutic purposes. However, the most frequent diagnostic examinations were thyroid uptake studies using radioactive iodine. At first, the amount of radioisotope administered was based upon experience and was determined by the need to detect sufficient gamma rays from the part of the body under examination (e.g. thyroid gland). Internal dose calculation techniques, such as the Manchester System,[31] existed for therapeutic implants of radium and radon as capsules, needles, or seeds. Dosimetry of the patient gradually began to develop as artificial radioisotopes became available. As it was several times higher than dose due to photons, initially, only the internal dose delivered by beta particles emitted by a uniformly distributed radioisotope was considered. L.D. Marinelli in 1942,[4] presented the first paper on the internal dosimetry of artificial radioisotopes.[21] An improved paper followed in 1948,[5] which clearly described the fundamental relationship between the concentration of beta-emitting radioisotopes in tissue and tissue-absorbed dose. In this publication, the assumption that metabolic elimination in tissue follows an exponential relationship with time, was introduced and the difficulty of obtaining biological data was clearly recognized. It also approached the problem of gamma dosimetry in an analogous way

and introduced a geometric factor, g, in centimeters that depended on both the size and shape of the tissue mass under consideration and the absorption of gamma rays. The value of g for a point, P, integrating for the total volume is

$$g = \int_v \frac{e^{-\mu\rho}}{P^2} dV \quad (\text{cm}) \qquad \textbf{(Eq. 1)}$$

where:

μ is the photon attenuation coefficient at source energy (cm^{-1}), and

p is the distance of volume element dV from the point P (cm).

The geometric factor g for a point at the center of a sphere is

$$g = 4\pi/\mu\,(1-e^{-\mu R}) \quad (\text{cm}) \qquad \textbf{(Eq.2)}$$

where R is the radius of the sphere.

The value of g for a point P at the center of a cylinder (which is a better approximation of the trunk of the human body) of radius R and height=2Z is

where:

$P+z^2 = p^2$ is the square of the distance between the point P and each elementary volume dV.

It was obvious that calculations of g for complex shapes and non-uniform distribution of radioactivity were extremely difficult, so calculations were limited to spheres, cylinders and ellipsoids.[2]

Many difficult problems for the calculation of geometric factors in internal dosimetry, were solved by W.V. Mayneord[6] using the reciprocal theorem first reported by L.V. King in 1912.[2] Using this relationship—i.e., the equations of integral dose from a point source of radiation to a volume are the same as those for the dose to a point from an extended source—Mayneord calculated the integral dose for a human phantom made of cylinders of various sizes.

Edith Quimby in her chapter on the "Dosimetry of Internally Administered Radioactive Isotopes" in 1951,[7] proposed the approximation of many organs by spheres and made two significant remarks: First, the Differential Absorption Ratio D.A.R. value (i.e., the ratio of concentration in a tissue to the average concentration in the body), previously published by Marinelli,[5] depends upon the time of measurement. Second, the question of what was the optimal time to compare the D.A.R for several organs did not have a definite answer.

In 1955, Loevinger described dose equations for internal dosimetry.[8] The beta dose equation required the average energy of the beta radiation, the effective half-time and the concentration of activity. The gamma dose equation included the exposure rate at a unit of distance from a point source of a unit of activity, the effective half-time, the concentration of activity and the geometric factor. He pointed out that the value of g was derived using a model for the representation of the human body and any dose calculation made would apply only to the specific model.

After 1960, computers that could perform repetitive complicated calculations were developed, and their speed and power of calculation gradually improved. The time was right for a calculative technique to take over and this was the Monte Carlo technique. This calculative method uses the probabilities of interaction and decides statistically the fate of a photon transported through a material. The procedure is repeated for every gamma ray until it is absorbed by the matter or penetrates the material and exits through its boundaries. If a great number of gamma rays are followed and their interactions recorded, results can be derived that simulate very accurately the real physical processes.

In January 1965, the Committee on Medical Internal Radiation Dose (MIRD) was founded,[12] recognizing as its primary goal to provide the medical and scientific communities with the most accurate estimate (in rads) of the dose received by a patient after administration of radiopharmaceuticals for diagnostic purposes. In 1966, Loevinger presented to the Committee a unified beta-gamma dose calculation method that constituted the first MIRD pamphlet.[5] Brownel, at the same time, proposed the use of absorbed fractions that were actually tabulated in MIRD Pamphlet No. 3.[13]

W. Snyder of Oak Ridge National Laboratory became a member of the MIRD Committee in 1968 and helped in the development of mathematical models of the human body and in the implementation of Monte Carlo codes in internal dosimetry. He also served as a link with the ICRP Committee that had an objective of estimating internal doses of workers for radiation protection purposes.[2] In 1968, Berger presented calculations of build-up factors for low-energy photons (<15 keV) and beta particles in tissue-equivalent materials.[11,12] Also, other types of radiation were investigated when, in 1975, the internal dosimetry of spontaneously fissioning nuclides was addressed[13] mainly for radiation protection purposes. The four major radiation components associated with spontaneous fission are due to neutron emission, gamma emission, beta emission and fission fragment

products. A detailed internal dosimetric model was developed separately for each type of radiation. A revised Pamphlet No.l, published in 1976,[14] extended the standard equations and introduced the use of "S-values."

MIRD Committee publications guided most of the nuclear medicine physicians and medical physicists around the world, and were utilized in the estimation of internal dose in a variety of cases. Many nuclear medicine departments became the centers for the collection of biologic retention and distribution data from humans. This data served as an input for several MIRD dose estimate reports published in the *Journal of Nuclear Medicine.* Most of these reports are based on the MIRD phantom, which includes male and female organs, and were developed initially by H. Fisher and W.S. Snyder.[15,16] A series of other mathematical models were created: for newborns, one-, five-, ten- and fifteen-year-olds,[1171 1S|] pregnant women during the nine months of pregnancy,[19] embryos receiving dose from the administration of radiopharmaceuticals to the mother during organogenesis[20] and for a variety of physiques of the Reference Man.

During the 1980s and early 1990s, revolutionary changes mainly in the field of medical imaging took place. The development of computerized tomography (CT), magnetic resonance imaging (MRI), single-photon-computerized tomography (SPECT) and positron-emission tomography (PET) improved the acquisition of data regarding the anatomy of patients, the physiologic functions as well as retention and distribution of radiopharmaceuticals. All of the above permit internal dosimetry to approach the true values of absorbed dose.

Modeling and methodology for the calculation of internal dose

The MIRD Schema

In 1968, the MIRD Committee proposed a complete and self-consistent system of absorbed-dose calculations in the scale of human organs (i.e. greater than a centimeter). This approach had been developed initially to answer the needs of radiation protection estimations in diagnostic imaging and took into account mainly gamma-emitting radionuclides. The MIRD methodology appeared in a series of pamphlets in supplements to the *Journal of Nuclear Medicine,* and also in two reference works.[21] The first, published in 1988 by Loevinger et al., is a summary of the proposed calculation methods[22] and the second, in 1989 by Weber et al.,[23] deals with the physical values appearing in the calculations.

The aim of internal dosimetry is to calculate organ doses so that risk estimates can be obtained for diagnostic or accidental administration of radionuclides as well as tumor and healthy tissue dose during under therapy procedures.[21] The MIRD schema attempts to calculate the mean absorbed dose, assuming an average tissue deposition of energy and a uniform distribution of the radiopharmaceutical.[24] The value of this dose can only be roughly estimated because its calculation demands the knowledge of a combination of physical and biological parameters not exactly determined. The dose is calculated for a target region r_k, by summing the contribution of each source region r_h to the target region and the contribution of the target region to itself. A source region is any region containing activity greater than the average concentration of activity in the total body. For non-penetrating radiation (beta particles, Auger electrons, internal conversion electrons and photons below 13 keV), only the radiation emitted within the target region is assumed to be absorbed. For penetrating radiation, all source regions contribute to the dose in the target region including radiation emitted by the target region itself.

If E is the energy absorbed in the elementary volume dV at distance x from a source which emits mono-energetic radiation of initial energy E_0, the absorbed fraction $(p(x,E_0)$ is a dimensionless parameter defined as

The specific absorbed fraction $O(x,E_0)$ is obtained by dividing the absorbed fraction by the mass dm of the volume dV and is expressed in g^{-1}. In particular, the specific absorbed fraction $\langle X \rangle (r_k \leftarrow r_h)$ (in MIRD notation) is the fraction of energy emitted in r_h that is absorbed in r_k, divided by the mass m_k of the target, i.e.

$$\Phi(r_k \leftarrow r_h) = \varphi(r_k \leftarrow r_h)/m_k \qquad \text{(Eq.4)}$$

The mean dose rate D in the target region r_k is obtained by the equation:

$$D(r_k \leftarrow r_h) = A_h \sum_i \Delta_i \Phi_i (r_k \leftarrow r_h) \qquad \textit{(Eq. 5)}$$

where:

A_h is the activity in the source region in microcuries, and

A, is the mean energy emitted per nuclear transition for the ith type of emission (previously called the equilibrium dose constant).

The quantity A, in units of g-rads/μCi-h takes into account the mean energy of the radiation of the ith type, the fraction of atoms which decay and emit the ith type of radiation and the constant of proportionality 2.13 which converts between MeV per nuclear transformation to g-rad/μCi-h . If E, is the mean energy in MeV of i type

particles emitted per transition and n, their mean number, then

$$\Delta_i = 2.13 n_i E_i \left(\frac{g \cdot rad}{\mu Ci.h} \right) \qquad \textbf{(Eq. 6)}$$

By integrating the dose rate equation, the mean absorbed dose during the time interval between t, and t_2 can be derived:

$$D(t_1,t_2)(r_k \leftarrow r_h) = \int D(r_k \leftarrow r_h)dt \qquad \textbf{(Eq. 7)}$$

Because the only time-dependent term in the dose rate equation is A_h, the calculation of the integrated dose can be achieved by using the cumulated activity A_h, instead of A_h, i.e.,

$$A_h(t1,t2) = \int A_h(t)dt \qquad \textbf{(Eq.8)}$$

To simplify the calculations, the S-factors, which are a combination of the above parameters, have been defined in M1RD Pamphlet ll.[24] S takes into account all the time-independent factors and is designated as the mean dose per unit of cumulative activity:

$$S(\mathbf{r_k} \leftarrow \mathbf{r_h}) = \sum_t \Delta_i \Phi_i (\mathbf{r_k} \leftarrow \mathbf{r_h}) / m_k \qquad \textbf{(Eq.9)}$$

So finally the absorbed dose is obtained by:

$$D(r_k \leftarrow r_h) = A_h S(r_k \leftarrow r_h). \qquad \text{(Eq. } \textbf{10)}$$

S-factors have been calculated for a variety of sources and target distributions in several anthropomorphic geometrical phantoms and tabulated for most of the nuclides that are used for medical purposes. These values depend, except for the phantom used, on the characterization of the emissions and of the method for the calculation of the energy transfer from source regions to target regions.[1211]

The M1RD formalism is today the most widely spread method for the calculation of absorbed dose in regions of the human body. Its basic advantages are its simplicity, the availability of physical and biological data for most radiopharmaceuticals currently in use, and the satisfying agreement between theoretical calculations based on the M1RD equations and experimental data. In cases where MIRD assumptions apply, MIRD formalism can be a useful and simple tool for the calculation of absorbed dose in every-day routine practice. However, the assumptions and limitations of the MIRD schema were the starting point for an onset of theoretical and experimental expansions and improvements. This article will attempt to summarize these developments, pointing out their basic elements.

Development of anatomical and physiological models

In the first MIRD pamphlets, the skeletal system and several organs were represented with the use of simple geometrical forms such as cylinders, cones and ellipsoids. From then up to now, the improvement and expansion of the range of phantoms available has not stopped, taking into account several different sets of parameters. For example:

- The heterogeneity of the body has been accounted for, by enlarging the materials of the phantom with soft tissues, bone and lungs with different compositions and densities.
- Distinction between the organ contents and the organ wall was made for certain organs such as the stomach and the bladder.

In determining internal radiation absorbed dose, it is frequently not possible to assume a uniform distribution of radionuclide in an infinite, homogeneous, absorbing material. The problem of non-uniform distribution of radionuclides within organs and tissues was approached by the development of several models taking into account the anatomical and physiological properties of a specific organ. J. Coffey et al., developed a heart model that divided the heart into chambers and muscle compartments.[251] J. McAfee described a model of the kidney that had a distinct cortex, medulla and collection system[1261] and also pointed out that the collection rate and changes in bladder volume would affect the radiation dose absorbed within the bladder. Later on, a dynamic bladder model was formed by Snyder and Ford[271] that accounted for these changes. In 1983, M. Lyra et al. [281] described a dynamic phantom of the kidney mimicking Tc-99m Glucoheptonate kinetics and measured the absorbed dose by TLD-100. A mathematical model of the peritoneal cavity was developed by Watson et al. [29] for calculating radiation dose to the major organs in the abdomen. In 1994, a model of the prostate gland was developed and included in the adult mathematical phantom within software to calculate the corresponding S-values.[30] A thyroid phantom was also used by M. Lyra et al for TLD-dosimetry of [31]I thyroid therapy and for the estimation of absorbed dose in ^{99m}Tc pertechnate thyroid scintigraphy.[31,321]

One of the most difficult non-uniform distributions is considered the external and internal irradiation of the bone and bone marrow, which was studied extensively by F.W. Spiers.[33] Some results appeared in MIRD Pamphlet 11, but the important contribution of the back-scattered radiation at the bone-soft tissue interface had not been

included. Dosimetry of the bone-marrow is essential because red marrow is often the dose-limiting organ during radioimmunotherapy.[211] Unlike most organs, bone marrow has neither a uniform composition nor well-defined boundaries. It has a variety of cells and it is distributed throughout various skeletal structures in the body, so it is extremely difficult to estimate the self-delivered dose. It is also extremely difficult to obtain an accurate value of the cumulated activity in the bone marrow. A proposed model was the representation of bone-marrow cavities as 400 ^m spheres surrounded by thick shells of 70 ^m to account for the bone walls.[1341] More recent developments in the dosimetric model[35] were integrated in the latest version of MIRDOSE3.[21] Dosimetry of the bone-marrow remains still an intricate and complicated matter and needs further investigation.

Development of bio-distribution models

For absorbed dose calculations, the time vs. activity relationship is needed. This can be integrated to give the cumulative activities in different organs and tissues. This can be achieved with the use of bio-distribution models. A bio-distribution model is based upon pharmacokinetic analysis and determination of the mechanisms that affect the distribution and transfer of the radionuclide in body tissues. This leads to a mathematical model, either compartmental or non-compartmental, which can be solved numerically and give the time-activity curve in every part of the body after administration of a labeled radiopharmaceutical.

Several bio-distribution models based on compartmental analysis were developed. Johnson and Carver[1361] presented a model that describes the uptake, retention and excretion of radionuclides in humans. The solutions to the model equations were numerical and based on the best fit of the model parameters to experimental results. This is useful when the intake of a radionuclide is not instantaneous or is not constant over a long period of time. In 1983, Wooten pointed out that if the patient data can be represented by a compartment model, it may be possible to calculate the activity in an organ without direct monitoring of that organ.[37] One can monitor another compartment and indirectly solve for the activity in the compartment of interest.

another instance, a comparison of the ICRP and MIRD models for iron metabolism in man showed that the MIRD model was more adequate for dosimetry calculations.[381] The ICRP model is a "once through" first order compartment model where the compartments are represented by organs (spleen, liver and other soft tissue), whereas in the MIRD model, physiological compartments are employed.

The development of the biokinetic model presents many difficulties in relating compartments to specific organs and tissues, and the presence of non-linear kinetics makes the models too complicated. However, strictly for internal dosimetry needs, a detailed biokinetic model is not always necessary and the time-activity curve can be derived alternatively—e.g., by directly measuring the fractional activity of a radionuclide in the organs of interest at different time periods after administration of radiopharmaceutical.

Experimental measurements for absorbed dose calculation

As has been said, internal dosimetry calculations are based on specific anatomical, physiological and biodistribution models which may not apply in each individual case. Experimental measurements for absorbed dose calculation may concern biodistribution data or direct measurement of the dose using appropriate radiation detectors and phantoms. Biodistribution studies are performed for the determination of the value of cumulative activity, especially in therapeutic applications; a low-radioactivity tracer dose is usually administered in a manner similar to the therapeutic procedures.[39] There are examples of using a radionuclide as a tracer—with the radionuclide having similar biodistributional behavior to the ones used for therapy, e.g., ^{99m}Tc-MDP for dose estimation in ^{89}Sr radiotherapy.[140,411] Biodistribution data are obtained collecting urine and blood samples together with organ and tumor radionuclide quantitation. For this radionuclide quantitation, one can use a probe, planar imaging or quantitative SPECT. Cumulated activity should be estimated for all organs with significant uptake as well as for the whole body and for tissues through which radioactivity is excreted.[42]

An example of correlating absorbed dose with bio-distribution data occurs in the use of impulse response function analysis for investigating the effect of varied strontium renal plasma clearance in patients receiving ^{89}Sr.[43] Tumor and bone marrow dose were shown to change by a factor of three as the strontium plasma clearance varied over the range observed in patients, Impulse response function analysis was found to be a powerful tool in finding the relationship between strontium kinetics and ^{89}Sr dosimetry. In

Apart from biodistribution studies, there have been several attempts to obtain experimental data for verification purposes of calculated values in mathematical phantoms. There were many difficulties and shortcomings in the comparison of experimental and calculational data, such as the phantom's physical characteristics, the organ locations, the dosimetric system, etc.[44] At first, small detectors were used for "point measurements," which were afterwards converted

to average organ dose. Nevertheless, the desired experimental data would be those obtained with a volumetric dosimeter, which could be shaped to represent the organs as specified in the mathematical phantom. With such a volumetric dosimeter, one could measure average absorbed doses over the entire organ and compare them directly with the calculated values.

In addition to its shaping ability, the dosimeter should be tissue-equivalent and sensitive to the low radiation exposures usually found in nuclear medicine. Sensitivity is necessary because low activity is also preferable for radiation protection reasons during the measurements. Other desired properties are a good response stability, reproducibility, a stability in aqueous media, and a reasonable cost. The choice of TLD materials suspended in organic compounds seemed to be the most justified.[1451]

Dosimeters that were a mixture of organic tissue-equivalent materials and LiF thermoluminescent powders were proposed.[1461] The initial material is a liquid introduced into the negative mold and rapidly solidified.

The molding technique used for the fabrication of the dosimeter should be of low cost and easily formed. Also, the fabrication and calibration of source organs is important, since the radioactive material must be contained by a mold of good rigidity to avoid radioactive leaks. Finally, the radiation field inside the phantom should not be affected by the construction materials of the molds.

Considering all of the above requirements, it can be said that there appear to be two fundamental directions in internal dosimetry experimental measurements. The first focuses on the extraction of data (biological, anatomical, etc.) for the specific patient. In this way, more realistic dose estimates can be achieved for cases differing radically from standard models, or for cases where the accuracy of absorbed dose is crucial.

The second direction is aimed at the experimental verification of theoretical models, leading to the improvement and expansion of the available models and phantoms, so that each individual case can be represented closely by an existing model.

Modeling of physical mechanisms related to internal absorbed dose

Macrodosimetry

As stated above, the M1RD schema implementation focuses on an average tissue deposition of energy. In this way, it estimates the mean radiation absorbed dose in a macrodosimetric scale of a target organ or a tumor mass,

At first, the characteristics of the radionuclides used for medical purposes were investigated and tabulated in MIRD pamphlets 4,[47] 6[48] and 10,[49] including decay schemes, energies and intensities of emitted radiations, In the case of beta-emissions, only the mean energy of the emission spectrum was utilized.

In the internal dosimetry of gamma-emitters, the geometric factor approach introduced by Marinelli et al.,[5] was proven to be a simple calculational tool. The assumption used in this method is that the effective absorption coefficient is taken as either 0 or 0.028 cm^{-1} (0 for linear dimensions less than 10 cm and 0.028 cm^{-1} for larger distances), independent of source energy. This was justified clinically for the case of radium, because the absorption coefficients do not vary significantly in the energy range of 0.1 to 1 MeV. However, the error in this assumption is important in the case of low-energy gamma-emitters (e.g., ^{125}I and ^{99m}Tc) utilized frequently in nuclear medicine.

Gupta et al.,[1501] modified the conventional geometric factor by replacing the effective absorption coefficient by the attenuation coefficient appropriate to the source energies and including the effects due to multiple scattering by using point-source dose build-up factors, The new modified geometric factor applied very well to the lower energy region where absorption coefficients change rapidly with energy. Later, the same author[51] presented a new correction to the geometric factor, taking into account the source shape effect that dominated in energies below 200 keV.

The presence of source-free regions in the source-target geometry of beta emitters was investigated by Brookeman et al.[521] The assumption of 100% absorption of non-penetrating radiation leads to overestimation of the absorbed dose. Electron dose reduction coefficients determined at several distances from the source surface were used to correct the value of electron dose derived from the general absorbed dose equation—___

A new interest in the simulation of the physical mechanisms involved in internal dosimetry resulted in the development of the Monte Carlo code. Each source photon is followed by tracing its successive interactions in

an infinite tissue medium. Random numbers internally generated provide the probability for each photon parameter—such as its initial direction, the type of interaction (i.e. photoelectric absorption, Compton scattering or pair production) and the direction of the scattered photon. This is repeated until a photoelectric absorption occurs or the photon energy is reduced below a cut-off threshold (e.g., 10 keV). Records are made of the position of its interaction as well as of the energy loss at every point of the medium and these data serve as input for different programs that calculate values of absorbed fractions, build-up factors and other parameters. For better statistical results, the spectrum of photons crossing a very thin shell at various distances from the point source is calculated, rather than counting the actual number of interactions that occur within the shell. From this spectrum, the probable energy loss by photons in that thin shell can be calculated using appropriate energy absorption coefficients.[531

In an attempt to more accurately derive the values of absorbed fractions for low-energy gamma-emitters in the energy range from 20 to 100 keV, calculations were made by Reddy et al., in 1967.'[54]' These calculations were carried out using the Monte Carlo method—taking into account the effect of multiple scatter. Results were given for central-source and uniform-source configurations in total-body phantoms ranging in mass from 10 to 100 kg. These expanded into a method that considered the contribution to the absorbed dose from both direct and scattered radiation and gave results in terms of absorbed fractions, specific absorbed fractions and dose build-up factors.[53!] Specific absorbed fractions and dose build-up factors were given for central point isotropic source and for various energies and distances from the source, in both finite and infinite tissue equivalent media. The effect of a boundary was found to lower the values of specific absorbed fraction and build-up factor only within a short distance from the boundary.

The use of S-factors has proved to speed up calculations of internal dose estimates but has created several difficulties. One such problem was that—except for the organs where most of the radioactivity was concentrated—a fraction of total radioactivity was distributed throughout the remainder of the body. However, the S-factor tables do not include the values obtained when considering the remainder of the body as a source organ. This was taken into account in several corrections that later revised to include absorbed fraction values for the remainder of the body irradiating target organs.[1555561]

Microdosimetry

To decide whether a specific kind of radiation is penetrating or non-penetrating, one must define the order of scale of dosimetry. Most beta-emitters used in medicine have a range of the order of magnitude in millimeters. On the other hand, the energy of most alpha-emitters used in internal therapy is about 4-6 MeV, which gives a maximum range of 40-80 (am. This means that on the millimeter scale, although one cannot characterize beta-emitters as non-penetrating, alpha-emitters could very reasonably considered as such. However, for a range of tens of micrometers, alpha-emitters are no longer considered non-penetrating.[2!|]

Frequent use of mono-energetic dose-point kernels, which are calculated from Monte Carlo codes, is made. From these we can obtain the variation in energy transferred at a specific distance from a mono-energetic electron point source. The most widely used Monte Carlo codes are ETRAN[1571] and EGS4[1581] which, however, cannot give accurate results for electron energies below 10 keV. The scaled point kernel $F(x/r_0,E_0)$ is obtained by

$$F\left\{\frac{x}{r_0, E_0}\right\} = 4\pi\rho x^2\ \Phi\ (x, E_0) \quad \text{(Eq. 11)}$$

where p is the density of the medium, r_0 is the range of electrons in the continuous slowing down approximation (CDSA) at energy E_0, and $O(x,E_0)$ is the specific absorbed fraction.

In 1969, Cole [59] tried to overcome the above energy limitations by establishing an experimental relationship between the electron energy (keV) and the electron range (|im). This could give results for beta emitters of low-energy Auger electrons (some 10 eV). Leichner[1601] recently presented a point-source function that is equally valid for photons and beta particles and is derived from a fit of Berger's tables for a wide range of photon and beta particle energies.

Microdosimetric techniques for absorbed dose calculations are invaluable where radionuclides are used in tumor therapy. In these cases, for the optimization of the therapeutical benefit, the irradiation must be highly selective. The micro-deposition of energy within the tumor cell mass is of primary importance and must be uniform for effective therapy. Alpha particles have the advantage of high linear energy transfer (LET) but due to their small range, they present a non-uniform macro distribution of energy. On the other hand, beta particles and photons deposit their energy more uniformly but are less effective for tumor-cell killing as they have lower LET. Also, of crucial importance is the

relationship between tumor size and the area of radionuclide deposition.[391]

Computational methods in internal dosimetry

Several computer packages have been created for use in internal dosimetry applications. A computer program offers the advantage of both standardization and speed of calculation of the absorbed dose estimates of all organs and in cases where more than one radionuclide is involved. Also, it offers the user the opportunity to change input data for several cases, e.g. biological data. As previously mentioned, the main difficulty in obtaining absorbed dose is the determination of the value of cumulated activity. When this value cannot be derived mathematically based on tracer kinetics, it can be determined experimentally by measuring the activity in organs that have a relevant tracer concentration at fixed time intervals.[61] Thus, an experimental time-activity curve is obtained—which by extrapolating to infinity and integrating, can give us a value of cumulated activity. The reliability of this value depends on the frequency and accuracy of measured data. This technique gives the opportunity of performing patient-specific calculations but it has the disadvantage of being time-consuming and fatiguing for the patient, as it requires a number of patient scintigraphic images.

An important step in computational dosimetry is the selection of a point-source kernel which is dependent upon the radionuclide (actually its emission spectrum), the absorbing medium, and the scale and resolution of the calculation. The point-source kernel is, in fact, a table of absorbed doses for several distances from a point source.[1621] There are a variety of dose-point kernels and their process of generation differs (e.g. experimental measurements, analytical or Monte Carlo calculations). The use of analytical dose-point kernels generally has the disadvantage of not taking homogeneities into account, unless the convolution procedure is applied in the spatial domain. Inaccuracy of absorbed dose appears in lung and bone regions due to the variance of photon/electron cross-sections and differences in scattering for soft, bone and lung tissue.[631]

The Monte Carlo technique is numerical and, utilizing different probability distributions for sampling, can follow-up the electron and photon transport over arbitrary boundaries and interfaces. It also allows calculations such as the energy distribution of photons and electrons in a specific point and distribution of absorbed dose within a volume.[631]

In 1976, Feller[1641] designed CAMIRD/II, a software package that employed the MIRD equations to calculate absorbed dose. It asked for the names of the desired source organs and their cumulated activities. Another program presented at the same time, MIRD-S, computed the absorbed dose starting from the experimental measurement of activity in the source organs and calculating the cumulated activity by integration of the experimental curve.[651] CAMIRD/1II, presented in 1980,[61] combined the above two programs and gave improved results in many cases, e.g. for organs with walls. The cumulated activity was replaced in this program by "residence time" T which is the ratio of the cumulative activity to the administered activity.

The S-factors, as they were published in MIRD Pamphlet No. 11, are tabulated for 20 organs and for more than 120 radionuclides. In the computational technique proposed by S. Hoory,[66] each table is stored in the computer in a square form matrix S of order (20 x 20). So in a generalized form, the matrix elements consist of the absorbed dose coefficients per unit cumulated activity for n different organs. Each element S^ of the matrix S stands for the average dose contribution of the source organ j to the target organ i, assuming that the radionuclide is distributed uniformly in the source organ. Thus, the diagonal elements of the matrix represent the average absorbed dose contribution from each organ to itself. The system computes the cumulative activities *AI* of the n organs utilizing data as the physical half-life of the nuclide and several biophysical factors related to it. These values construct the cumulative activity vector A. The average dose estimates for the n organs form the organ dose vector D. Therefore, vector D can be obtained by multiplying the matrix S by the column vector A.

The Radiation Internal Dose Information Center (RIDIC) at the Oak Ridge Institute for Science and Education (ORISE) has been distributing various versions of a software package called MIRDOSE since 1987.[67] MIRDOSE performs internal dose calculations according to the MIRD technique for many radionuclides commonly used in nuclear Medicine. Its main purpose is to perform the calculations that are needed to obtain dose estimates for the various organs of the body once the kinetics of an agent are established and the residence times or areas under the time-activity curves for the various source organs are also established.

MIRDOSE 3 includes several widely accepted standardized models or techniques, including a dynamic urinary bladder model, the ICRP 30 GI tract model, corrections for remainder of the body activity, and a model for calculating self-dose to small, unit-density spheres (such as tumors). In addition, it contains a new bone and marrow model, developed by Keith Eckerman of ORNL. This model gives not only an average dose to red marrow from an agent, but also gives the distribution

of that dose throughout the skeleton for all 10 individuals modeled.

In 1999, MIRDOSE 3 contains 10 different models of the human body—one for adult males and females, one representing children of five different ages and 3 for the adult pregnant woman. It has 240 radionuclides available, calculates doses from up to 28 source organs to as many as 27 target organs, and reports the effective dose equivalent (ICRP 26/30) and effective dose (ICRP 60) for any agent studied.

Computational techniques form a crucial part of radionuclide treatment planning. In 1990, Sgouros et al.,[1621] used standard cumulative activity data projected over patient-specific anatomical data to develop a 3-D treatment planning program for internal radionuclide therapy. For purposes of therapy by radionuclides, the accuracy of calculated dose is crucial, because the consequences in radiation-sensitive tissues may be a limiting factor for the application of therapy. The input required consists of a point-source kernel for the specific radionuclide that can be selected from the stored data, a series of contours from patient CT scans that comprise a three-dimensional matrix which defines one or more source volumes, a corresponding matrix of independently obtained values of cumulative activity and a target plane, preferably one that intersects a therapy-limiting or target tissue. The point-source kernel is convoluted with the source volume cumulative activity distribution, and yields a two-dimensional matrix of dose values corresponding to points on the target plane, which in turn is converted into isodose contours that are presented superimposed on CT images.

Instead of using standard radionuclide distribution data, attempts have been made to use quantitative SPECT images for accurate tumor dosimetry. Koral et al.,[1681] employed skin markers to achieve the fusion of computed tomography (CT) and SPECT image sets, in this way allowing SPECT imaging procedure including patient-specific attenuation correction, to become quantitative. Patient anatomy and radionuclide distribution are combined into a three-dimensional internal dosimetry software system (3D-ID) developed by Kolber et al.[691] Here also, appropriate alignment is made between images of radionuclide distributions (PET/SPECT) and anatomic images (CT/MRI). In 1997, Akabani et al., presented an alternative method of a three-dimensional discrete Fourier transform convolution utilized together with quantitative SPECT reconstruction for dose calculations.[170,] Comparison of this method with Monte Carlo transport calculations gave satisfactory agreement.

Increasing interest and challenges for more accurate internal dosimetry calculations also presents the rapidly developing area of radioimmunotherapy (RIT). A software program[71] has been used successfully to calculate absorbed dosed for RIT treatment planning of Mabs radiolabeled with ^{131}I and ^{67}Cu for the treatment of lymphoma and breast cancer and can be extended for many of the standard radiopharmaceuticals that are routinely used in clinical nuclear medicine. It is based on quantitative Anger camera imaging that provides the data which, after fitting to linear, mono- and bi-exponential and cubic spline functions, model the biological accumulation and clearance of the Mab. Residence times for each source organ and radiation absorbed dose to a target organ is then calculated according to the MIRD protocol.

Current limitations in the derivation of absorbed dose

Uncertainties in the calculation of the mean absorbed dose for an organ or tissue are due mainly to uncertainnties in the S-value and the value of cumulated activity.[721] There may be some difference between planned and actually administered activity, although this is considered a minor uncertainty. Physical data included in the S-value—such as the yield and energy deppsition in the target organs—is considered fairly accurate. However, the use of S-factors may introduce significant inaccuracy in the absorbed dose estimates regarding the anatomical data of the patient, because the shape, position and mass of an organ differ from one human to another and the distribution of radioactivity is usually non-uniform. Moreover, the kinetics of an organ system may not be the same in response to a therapy dose as in response to a tracer dose.[37,] Therefore, quantitative uptake measurements must be obtained during therapy, which is more demanding on the imaging technology (due to high count rate) and requires the use of special collimators and suitable algorithms for dead-time correction.

The kinetic models used introduce several inaccuracies as the effect of abnormal physiology in the value of cumulative activity (e.g. abnormal renal function). Although modeling efforts have been made in this direction, biokinetic data are not ambient and usually come from healthy volunteers. There is generally insufficient information about the relationship between uptake of the radiopharmaceutical and clearance of age, sex, diet and drug therapy (e.g., use of diuretics). Organ-absorbed doses calculated for pediatric phantoms had to be based, until recently,[67,73] on adult biokinetic data. Uncertainty of uptake and distribution becomes more important for short-lived radionuclides.[42]

Several uncertainties are generated in the calculation of internal absorbed dose, even under optimal conditions. The MIRD method for calculating radiation absorbed doses to a "Reference Man" from internally administered radionuclides has some important inherent limitations as follows:

- uncertainties in cross-section values that produce systematic errors;
- a finite number of photon histories is traced by the Monte Carlo code, so sampling errors exist; and
- photoabsorption is ignored and all charged particles are assumed to deposit their energy at the site of interaction.[1441]

Uncertainties introduced in the calculation of S-values are coming from radionuclide energy yield, tissue energy absorption and anatomy-dependent factors. The M1RD schema assumes a uniform distribution of activity, which is not true for radionuclides emitting low-energy Auger electrons that have a variety of ranges from subcellular to multicellular dimensions. Therefore, distribution of radioactivity in an organ can lead to very high doses in individual cells.'[421]

The imaging system also has some inherent uncertainties such as resolution, septa! penetration, detector uniformity of response and dead time and camera sensitivity. During the processing of data, several errors are introduced—e.g., counting statistics, organ/tumor region definition, background subtraction, attenuation and scatter compensation.'[711]

Quantitative SPECT images have a limited application for small volumes due to the limited spatial resolution of SPECT system and also the scatter conditions affect the numerical values. Reconstruction parameters such as attenuation correction algorithms can also distort the relationship between the counts in each pixel/voxel of the image and the radioactive concentration in the object. Moreover, the calibration data (i.e. imaging of appropriate phantom with known radioactive concentration of the tracer to obtain counts/activity relationship in clinical imaging) may include inaccuracies.'[74,751]

Conclusion

This article has attempted to summarize the basic concepts of internal dosimetry and follow its development up to recent years in various fields, such as geometrical and biological modeling, simulation of particle interactions with matter and computational techniques. Apart from diagnostic imaging, using radionuclides in nuclear medicine for therapy purposes has increased the requirement for accuracy in calculating absorbed dose. However, in spite of the progress made, the existing limitations permit only an estimate of the value of absorbed dose. Microdosimetric techniques and development of computational methods give hope of increased accuracy in internal dosimetry in the future.

Although absorbed-dose estimates are important in diagnostic applications for the implementation of ALARA principle in patients, dose calculations are crucial for planning of the treatment process in nuclear medicine and therapeutic applications. Especially in radionuclide therapy, it is important to calculate the dose utilizing data of the specific patient, such as the anatomy of the organs and size and localization of tumor. Although modeling procedures of biological and physical mechanisms have gone a long way in determining internal absorbed dose and are still perfected, we have passed to the era of patient-specific dosimetry, especially where therapeutic doses are involved. This trend will also be enhanced by the rapid development of computing techniques and quantitative medical imaging.

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