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Dosimetry of Internal Emitters: Past, Present and Future

A . R . R e d d y
Defence Laboratory, Jodhpur-342 001
M.M. Gupta
Institute of Nuclear Medicine and Allied Sciences, Delhi-110 054
and
A. Nagaratnam
Defence Metallurgical Research Laboratory, Hyderabad-500 258

ABSTRACT

Dosimetry of internal emitters is entirely a post-war development. From the first definitive paper on the subject appeared in 1948 to the present day MIRD schema, there has been a continued advance in our knowledge of radionuclide decay data, radiation interaction cross-sections, computational methods for obtaining absorbed fractions, mathematical description of anthropometric models, collection and analysis of biokinetic data of internal emitters.

After listing out the developments in radiation dose units, the present review briefly summarises the physical and biological bases of the estimation of the mean organ radiation dose, specifically mentioning the contributions from the Institute of Nuclear Medicine and Allied Sciences. The shortcomings of the conventional 'mean organ dose' concept have been brought out, highlighting recent developments in local dosimetry and microdosimetry. The expected potential future developments in dosimetry of internal emitters are also enumerated.

1. INTRODUCTION

Dosimetry of internal emitters is a mature branch of radiological science with a rich heritage, a well-established present, and holding out bright prospects for the future. The first paper on this subject based on the concepts of specific gamma ray constant and geometric factor was published in 1948 (Quimby'). The present review lists out the salient developments in dosimetry prior to the era of absorbed fractions and briefly brings out the significant contributions made by scientists from INMAS (Institute of Nuclear Medicine and Allied Sciences) in applying absorbed fractions

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for practical dosimetry in various nuclear medicine procedures and in computing HILED (highly localised energy density) dosimetry. It also enumerates the areas in which the future of internal dosimetry lies, particularly in finding the radiobiological significance of microdosimetry.

2. DEVELOPMENTS IN PRE-ABSORBED FRACTION ERA

2.1 Units of Radiation Dose

1906: Eve suggested an indirect approach to the measurement of the energy absorbed in a tissue medium, namely, the determination of the number of ion pairs produced during the absorption of the radiation and the energy absorbed per ion pair[2]. Hence it is important to note that Eve has anticipated the basic ideas of both the units roentgen and rad which were introduced much later.

1911: Mme Curie prepared a standard of a carefully weighed and analysed sample of a radium salt[3]. Specifications were made in terms of milligrams of radium element.

1919: Regaud, a leading French doctor who was using radium for therapy, called attention to the differences between emitted, delivered, and absorbed doses, but admitted that the only unit that could be used at that time was milligram-hours[3].

2.2 Biological Units of Dose

1918: Russ proposed the first biological unit of radiation[4]. Defined as the amount of radiation necessary to kill mouse cancer cells, this experimental quantity was called rad.

1919: Ghilarducci suggested the amount of radiation required to produce ulceration in the intestines of rats[5]. Another alternative was the killing dose for small biological organisms such as *Ascaris* or Drosophila eggs. Perhaps the most practical parameter was the amount to produce erythema on the human skin.

None of the above biological experiments or suggestions could be standardised in view of the wide variability and strong dependence on various physical factors. Hence it was realised that a chemical or physical reaction would be preferable to a biological one.

2.3 Physical Units of Radiation Dose

1913: Rutherford and Robinson made the first attempts to measure heat resulting from absorption of radioactive radiations in a small region[6]. But the attempts were not successful.

1920s: A unit, roentgen, had been developed for x-rays in the 100 to 200 keV region, which offered a beginning for dose standardisation with x-radiations. Gamma radiation from a point source of radium had also been measured in terms of roentgen. To be more specific, the value ranged from 8.4 to 8.6 R per milligram-hour from a point source of radium at a distance of 1 cm. The unit roentgen was officially adopted by the International Congress of Radiology in 1928.

1922: Quimby prepared tables of data of the dose delivered for about 200 applicator sizes and distances[7].

1947: Meredith calculated tables of data in terms of number of milligram-hours necessary to deliver 1000 R at the point in question'.

1948: Paterson and Parker calculated a value of 8.4 R per milligram-hour for a point source of radium at 1 cm distance[9]. This is called the dose delivered.

2.4 Radiation Dose From Radioactive Substances

1941: Marinelli published the first approach to the problem of radiation'dosage from a radioactive material", viz., ^{32}P. He invented a new unit, which he called the equivalent roentgen, resulting from total decay of a particular amount of radionuclide in one gram of air which would result in the same number of ion pairs as would be produced when it is exposed to 1 R of x-rays. In order to obtain the dose to a patient or a particular tissue, it is necessary to determine the number of beta particles released per unit volume (or unit mass) of tissue.

1948: Marinelli, et *al* published the method of dosage calculation for other radionuclides, wherein they introduced the concept of 'effective half-life' to take into account the influence of physiological excretion of the nuclide in addition to its physical radioactive decay". Dose was still expressed in terms of roentgens and it was called as dose delivered (in present day understanding exposure). The same authors introduced a new parameter called 'specific gamma constant' for gamma dosimetry. It was expressed as the exposure in roentgens at 1 cm distance from a uniform point source of 1 mCi in air during 1 hour and was calculated for a number of radionuclides.

Early 1950s: A new unit, called the rad, which is equal to 100 ergs absorbed per gram of the absorbing material, was invented to express the parameter dose absorbed. Thus if the radionuclide concentration in the target of interest is known, absorbed dose, from either beta particles or gamma photons or from both, could be calculated from the above information.

1964: 'Absorbed fraction' was defined by Ellett, Callahan and Brownell[12]. Its values for a number of geometries of different sixes and for different photon energies computed by Monte Carlo method have been published.

1968: A new era of internal dose for biologically distributed radionuclides began with the acceptance of the schema proposed by Loevinger and Berman[13] to MIRD (Medical Internal Radiation Dose) Committee of the American Society of Nuclear Medicine, and with the publication of MIRD schema as well as data on dose build-up factors (Berger[14]) and data on. absorbed fractions by Brownell, -et *al*[15] as MIRD pamphlets. Subsequently, data on radionuclide decay schemas, 'reference man', 'specific absorbed fractions' as well as S-factors for a large number of source and target organs of the reference man have been published as MIRD pamphlets. The MIRD schema has provided a unified approach for dose estimate for any type of radiation and target well as source organ, thus scoring a great advantage over the Marinelli-Quimby-Hine formalism of 1948.

2.5 Physical Basis of Internal Dosimetry

The Marinelli-Quimby-Hine system" of internal radiation dose calculation was based on distinguishing the radiation as penetrating and non-penetrating. Gamma photons are examples of penetrating radiation and electrons are non-penetrating radiation. For non-penetrating radiations, all the energy is assumed to be absorbed in the target, unless the target of interest is much smaller than the range of electrons emitted. Calculations of ^{131}I dosimetry in small spheres have taken into consideration the partial absorption of beta radiations[16,17]. For photons, two parameters, viz.,

'gamma ray exposure rate constant' (Γ) and 'average geometric factor' (g) are considered. The former encompasses (roughly) radionuclide decay characteristics as well as the photon energy absorption coefficient in air or tissue of interest and is expressed in R/mCi-hr at 1 cm from a point source. The parameter average geometric factor, $\bar{g}$, is to take care of shape of the target in which the source is uniformly distributed. Here it is assumed that the photons (both primary and secondary) can be represented by an 'effective absorption coefficient', μ_{eff} equal to either zero (when the target has linear dimensions less than 10 cm), or 0.028 cm-' when it is larger. These assumptions are valid when the emitted photon energy is greater than a few hundred keV. Focht, et *al* calculated the values of $\bar{g}$ for spheres and cylinders of different sizes[18] Tables of gamma ray exposure constants for commonly used radionuclides; are also available".

3. ABSORBED FRACTION ERA

Absorbed fraction system of Marinelli, *et al*[11] has been extensively used for dosimetry of internal emitters until recently. However, with the increasing use of low energy photon emitters (for example, ^{99m}Tc) for nuclear medicine procedures, questions have been asked about the validity of the assumption of an effective absorption coefficient of either 0 or 0.028 cm-', whatever the target size or photon energy is. The argument is valid in view of the rapid variation of the linear absorption coefficient with photon energies less than 100 keV. Satisfactory solutions to these arguments have become possible with the availability of detailed photon interaction data compilations at the National Bureau of Standards, USA, and advanced semi-analytical computational techniques on large computers. The pioneering papers of Ellett, Callahan, Brownell and Reddy first introduced the concept of 'photon absorbed fraction' and its computation using Monte Carlo techniques for regular geometries (such as elliptic cylinders, ellipsoids, spheres, straight cylinders, etc) of different sizes having either point or uniform source distributions emitting photons of energies from 20 keV to 2 MeV[12,20]. Using more sophisticated sampling techniques Snyder, et *al* at Oak Ridge National Laboratory obtained absorbed fractions for a homogeneous tissue equivalent mathematically defined anthropometric phantom[21].

To establish a uniform method of radiopharmaceutical dosimetry, the Society of Nuclear Medicine of USA formed MIRD Committee which brought out its first pamphlets in 1968[13-15]. In MIRD Pamphlet 1, Loevinger and Berman[13] formulated a schema for internal dose estimation based on the concepts of 'absorbed fraction' and 'specific absorbed fraction'. Minor revisions to the above were brought by the same authors in 1976.

The schema may be outlined as follows: Radioactive materials administered to a patient are distributed in the various body regions, $r_1, r_2, \ldots r_h$. Regions can be points, lines, surfaces or volumes. Certain portions of the body may be considered as 'target' volumes, these being designated by v. The average absorbed dose in v from r_h is-equal to the energy absorbed in v which originates in r_h and is symbolised by $D\ (v \leftarrow r_h)$, given by:

$$\bar{D}\ (v \leftarrow r_h) = \tilde{A}_h\ (t_1, t_2)\ \Sigma\ \frac{\Delta_i\ \Phi_i\ (v \leftarrow r_h)}{m_v}$$

$$= A_0 \tau_h\ S\ (v \leftarrow r_h),$$

where A_h (t_1, t_2) is the cumulated activity in μCi hr given by $\int_{t_1}^{t_2} A_h(t)\,dt$; Δ_i is the equilibrium dose constant or mean energy emitted per unit cumulated activity in g rad/μCi hr; Φ_i ($v \leftarrow r_h$) is the fraction of radiation energy of type i released in source region h, and absorbed in target v, m_v is the mass of the target v in g; A_0 is the activity administered to the patient, τ_h is the residence time, and $A_0\tau_h = A_h$ (t_1, t_2); $S(v \leftarrow r_h)$ is the mean absorbed dose per unit cumulated activity in rad per&i hr.

MIRD Committee systematically collected and published data that pertain to different parameters of the above dose equation. Radionuclide decay data for computation of Δ_i for more than 100 radionuclides have appeared[22] as MIRD Pamphlet 10. Photon absorbed fraction data for regular geometries of different sizes, homogeneous tissue equivalent medium, and uniform source distribution have been the subject matter of MIRD Pamphlets 3 and 18[15,23]. Values of S-factors for a heterogeneous anthropometric adult reference man phantom for different source locations were listed-in MIRD Pamphlet 11 for 117 radionuclides[21]. Electron absorbed fraction data for monoenergetic point electron sources or beta emitters were tabulated" in MIRD Pamphlet 7.

To facilitate calculation of radiation doses to different age groups, mathematical phantoms have been developed for the age groups of 0 (new-born), 1, 5, 10 and 15 years. S-factors have been computed 'for a number of targets containing radioactivity in different age groups. A variety of computer software systems have been developed for the users of time-sharing or minicomputers for computing internal radiation doses,

Parallel to these developments of unified MIRD schema based on the concept of absorbed fraction, simpler methods of refining the parameters of Marinelli, et *al* dose equation have been evolved. One such refinement developed at INMAS was to introduce the 'modified geometric factor' approach[25]. In this method, using the linear attenuation coefficients of each photon energy and dose build-up factors for each of the source-to-target distances, the. limitation of the earlier effective absorption coefficient is minimised. Tables of average geometric factors and absorbed fractions derived therefrom have been published for spheroids of a variety of sizes and eccentricities. Reddy and Mehta have extended the lower limit of the photon energy to 1 keV and spherical target sizes of micron dimensions[26].

At this point it must be emphasised that all the physical data tabulated so far, either based on geometric factors or absorbed fractions, are for specific mathematically defined models. Therefore the dose estimates at best to these models are to be used only as guidelines for humans.

3.1 Biological Basis of Internal Dosimetry

The parameter that comprises the biokinetic behaviour of the internal emitter is the cumulated activity A_h (t_1, t_2) expressed in μCi-hr. The same parameter was split into three, viz., activity administered, fractional uptake, and effective mean life (1.44 times the effective half-life) in the Marinelli-Quimby-Hine dose formalism. The cumulated activity A_h in a region r_h can be described mathematically, based on a measured set of data points at different times. For- a number of internal emitters, ICRP published the biological data required for calculating A_h based on multi-exponential and power function fits. Kaul, et *al* have compiled the available biokinetic data for several radiopharmaceuticals". MIRD Committee also collected biokinetic data for different radiopharmaceuticals and analysed them by sophisticated

simulation techniques to get the cumulated activities. The Committee has brought out summary dose estimate reports for several radiopharmaceuticals[28].

However, appreciable alterations in the data are produced in case of pathology intrinsic to the organ of interest. For example, with ^{131}I-Rose Bengal, the estimated T_{eff} in normal and hepatitis cases are respectively 0.062 and 2.2 *d*; the consequent absorbed doses (rad/mCi) are 12 and 440 respectively. In case of intrahepatic disease, the per cent administered activity in urine was 30 as against 25 per cent in normals. Hence the consequent absorbed doses are 4.67 and < 0.78 rad per mCi respectively. Such appreciable alterations in metabolism are also observed in patients undergoing radiotherapy and chemotherapy[29].

At this stage it might be concluded that there exists a sound physical base for accurate internal average dose estimates to model organs under the MIRD schema. Although sophisticated computational methodologies for analysing biokinetic data of radiopharmaceuticals exist, the basic availability of data itself is scanty, more so for humans.

3.2 Efforts at INMAS

During this period significant contributions to dosimetry of internal emitters were made by scientists from INMAS with active encouragement from the late Brig. Mazumdar. Sastry, et *al* estimated radiation doses from (i) a chelating agent like DTPA labelled with ^{113m}In, ^{111}In, and ^{169}Yb used for kidney function and brain scanning, (ii) ^{113m}In iron hydroxide macroaggregates used for lung scanning in different age groups, and (iii) ^{113m}In colloid used for liver scanning in different age groups[30].

Sastry, et *al* have estimated radiation doses from ^{131}I-HSA, ^{123}I-HSA, ^{99m}Tc-HSA and ^{113m}In chloride used for placental investigations to ascertain the relative merits of the different radiopharmaceuticals[31]. They have also estimated radiation doses to different organs of both mother and fetus. Reddy in collaboration with Elasser, et *al* has computed specific absorbed fractions and S-factors for calculating absorbed dose to embryo/fetus and has presented the dosimetry of fetal tissues for ^{131}I and ^{59}Fe using biokinetic data for various stages of pregnancy[32]. Reddy and Mehta have recently reviewed[33] the information available for estimating embryo/fetus dosimetry in situations where the radioactivity was inadvertently administered to pregnant women (who were not aware at that time that they were pregnant) and presented as an example a case study of ^{131}I administered to a patient of thyroid cancer in such a situation.

As early as 1971, Sastry, et *al* reviewed radiation doses in paediatric radioisotopic investigations and presented absorbed fractions as a function of age for various energies along with a summary of the radiation doses for different age groups received by the whole body and specific organs for some commonly used diagnostic tests".

4. POST-ABSORBED FRACTION ERA

The concept of mean organ dose and the method of calculating it by MIRD schema are valid only if it is assumed that the activity is uniformly distributed throughout the source region. When viewed macroscopically, the assumption is valid for most of the nuclear medicine investigations and hence the mean organ dose is taken as an index of the potential hazard due to the radioisotopic investigation.

However, with the availability of sophisticated experimental methods of determination of microscopic localisation and biokinetics of the administered activity combined with complex mathematical models of the organ and a variety of computer methodologies, the dosimetry can be made at any level to a target of interest. But at what level should the dosimetry be done? Is the conventional calculation of absorbed dose at the organ level, assuming a uniform concentration of radionuclide, not sufficient? Or should we go down to the assumed models of tissue, cellular and even subcellular structures? Reddy, *et al* examined the problem in detail taking ^{131}I vs ^{125}I in thyroid, ^{203}Hg vs ^{197}Hg neohydrin in kidney, and thorotrast (^{232}Th) in liver as examples[35]. Significant differences between the mean organ dose and dose to a relevant microstructure (such as apical membrane in the cells of thyroid follicles in case of thyroid, epithelial cells lining the proximal tubules of the cortex in the case of the kidney, and nuclei of cellular structures in reticuloendothelial system of liver) were found.

Reddy and Kaul have computed detailed microscopic dose distributions across thyroid follicles of varying sixes for a number of radioiodine isotopes". The radiobiological significance of ^{125}I microdosimetry has been the subject of another study by Reddy and Nagpal[37]. They have brought out the radiobiological differences due to ^{131}I and ^{125}I in rat thyroid using one month old rats 'instead of adults. As these normal young rats grow to three months age their thyroid weight increases by about three times. This increase in thyroid weight is largely due to cell proliferation and should be hampered to varying degrees for the same mean gland dose from ^{131}I and ^{125}I. The effect of radiation on the thyroid cell proliferation can therefore be studied directly without the use of a goitrogenic challenge. Different doses of ^{125}I and ^{131}I were administered.to different groups of one month old rats. They were then monitored for their body growth and thyroidal radioiodine retention for a period of two months. At the end, a tracer dose was administered to determine the 24-hr thyroid uptake. The animals were then sacrificed, their thyroids weighed, and the percentage uptake determined. The thyroidal weights were converted into percentage cell survivals. When compared between 100 μCi of ^{125}I and 71 μCi of ^{131}I, the body weight was impaired more with ^{125}I, whereas the 24-hr uptake was significantly reduced with ^{131}I. The 50 per cent cell survival dose with ^{125}I was about two times that with ^{131}I.

With a view to see whether the non-homogeneity of radiation dose distribution at the microscopic level with ^{125}I has a different ultrastructural effect on the follicular cell compared to ^{131}I, Puri, *et al* made an electron microscopic study of the time course of radiation effects on rat thyroid using 50 μCi of ^{125}I and ^{131}I each[38]. The mean dose delivered to the thyroid gland with 50 μCi of ^{125}I was 7500 rad and that with ^{131}I was 22,000 rad. Though there is a marked inhomogeneity in dose distribution across the follicular cell in the case of ^{125}I, the ultrastructural changes observed with both isotopes were, in general, similar. The most affected part of the follicular cell was the apical membrane which was followed by the alphacytomembranes. Although the radiobiological and dosimetric basis of ^{125}I therapy of hyperthyroidism was quite encouraging (leading one to expect that late onset of hypothyroidism, a frequent concomitant of ^{131}I therapy, could be minimised), clinical trials using ^{125}I have not been successful[39].

In spite of this failure, microdosimetry of ^{125}I and many other Auger electron emitters has remained a subject of recent research in view of their success as suitable labels that could target on to any part of a cell. The subject received further impetus

and importance with labelled monoclonal antibodies coming up as potential immunoradiotherapeutic agents for tumour therapy. The status of the local dose estimates and the microdosimetry of Auger electron emitters have recently been reviewed[40]. For a number of radionuclides the mean energy deposited per decay in microspheres having radii in the range of micrometers to nanometers has been computed. Details of the variations in the intensities of the emitted radiations in' individual radionuclide decay, energy depositions due. to each emission in the microtargets of interest, as well as the energy transfer due to charge migrations along the molecule in which the radionuclide has decayed, have been considered in order to obtain the relevant dose and assess its potential-biological effect.

5. FUTURE TRENDS

Researchers concerned with radioactive substances have always striven to get better and better estimates of the radiation absorbed dose; particularly so in the field of medical applications of radiation and radionuclides. The real goal of the dosimetrist has been to clarify the relationships between interaction of radiation with matter and the biological effects. Important physical information inputs for such a goal are: (i) detailed knowledge of the. source region, such as it size, geometry, composition molecular nature, etc., (ii) the details of radioactive decay, such as type of radiations emitted, their energies and yields, and (iii) details of the interactions of the above radiations with the source materials, such as radiation interaction cross-sections, transport equations, and techniques to compute the energy deposition in the source region or any other region of interest, and probability distribution of interaction events that result in energy deposition. While these are fairly straightforward, albeit complex and tedious to obtain, the biological information-such as temporal kinetics of the radionuclide in the source region, consequences of radioactive decay at the site of decay and surroundings due to transmutational changes-has remained complex. With the availability of radioactive labels to tag any part of a cell, the situation has become more difficult.

It appears that in future, the following programmes will receive wider attention and solutions have to emerge:

(a) More concerted efforts to collect biokinetic data for all radiopharmaceuticals, including those with ultra-short half-lives, for normal human model, disease states, medication, lactation, age, sex, use of blocking agents, etc.

(b) Embryo/fetus dosimetry which requires definition of a suitable model of the embryo/fetus weight vs its gestational age arriving at an age-dependent anthropometric model for embryo/fetus;. estimation of the transplacental cross-over of the radionuclides administered to the mother. Information on this latter aspect is next to impossible to get in view of ethical and medico-legal considerations. However, appropriate animal models may give some answers.

(c) The confusion between conventional dosimetry, millidosimetry, microdosimetry and nanodosimetry will have to be sorted out. Basically, all these forms of dosimetry are the same and adhere to the MIRD schema of Loevinger and Berman. Energy deposited. in a region due to a radioactive source decaying in it is the parameter of interest. The linear dimensions of the region of interest begin shrinking from mm to μm to nm depending upon

the identification of the biologically significant target, deposition of a certain amount of energy in which causes the measured effect-for example, from an organ to its tissues, to its cells, to its nucleus, and from nucleus to the DNA. Such local or HILED (highly localised energy density) dosimetry (common terms alternately used for milli, micro or nanodosimetry) estimates have mostly 'been non-stochastic or mean dose values. As per many studies involving Auger electron emitters used as labels to DNA or plasma membrane or to any other part of the cell, the energy deposited in that target correlates well with the biological effects (mostly cell survival or DNA strand breaks observed). Will the future hold the same prospect?

(d) Stochastic nature of radioactive decay and the consequent stochastic nature of energy deposition in targets of smaller and smaller dimensions are being worked out. The probability distributions of the specific energy imparted to such targets have been computed for some electron emitters and some alpha emitters. This methodology, called microdosimetry (entirely different in concept from the microdosimetry mentioned earlier), also calculates the number of targets that would not receive any energy deposition at all, in addition to the probability distribution mentioned above. The radiobiological significance of this microdosimetry is still not clear. Microdosimetry of external radiation beams, (proposed nearly 25 years ago) is being appreciated now in the protection range and niicrodosimetry counters adhering to ICRU norms have been designed and are in use. Will it take that long a number of years for microdosimetry of internal emitters to find relevance? It should be mentioned that in the case. of Auger electron emitters, energy deposition around the site of radioactive decay is highly intense and localised, and hence really no probability distributions can be worked out; since the amount of radioactivity available in the source region is small, the process of radioactive decay as well as the intensities of different radiations (including Auger, Coster-Kronig electrons) emitted consequent upon decay will certainly exhibit widely distributed probabilities.

(e) With the advent of monoclonal antibodies, particularly labelled with alpha emitters or Auger. electron emitters, prospects for radioimmunotherapeutic drugs seem to be increasing. The coming years promise large strides in the microdosimetry of this new class of radiolabelled antibodies.

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