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REPORT NO. 3 OF AAPM
NUCLEAR MEDICINE TASK
GROUP NO. 6

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Dosimetry of Auger-electron-emitting radionuclides: Report No. 3 of AAPM Nuclear Medicine Task Group No. 6[a)]

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The biological effects of Auger-electron-emitting radionuclides can be as severe as those of alpha particles of high linear energy transfer. A great deal of effort has been expended in exploring the biological effects of Auger electron emitters. Much of this effort has been devoted to improving theoretical and experimental techniques required to calculate absorbed doses and correlate them with the observed biological effects. Given that the main purpose of dosimetry is to obtain a physical descriptor with which to correlate radiation toxicity, then nowhere is this challenge greater than when biological specimens are subject to Auger electron cascades. The dense shower of short-range Auger electrons released by radionuclides, which decay by electron capture or internal conversion, results in biological damage that is highly dependent on the location of the decay site within the cell. In this report, different approaches to Auger electron dosimetry are described and compared. Methods to calculate the absorbed dose from Auger electron emitters at the DNA, cellular, multicellular, and organ levels are described as they relate to the biological effects. The concept of a radiation weighting factor for Auger electrons to be used in the calculation of equivalent dose is reviewed. The importance of subcellular distribution of Auger emitters in determining the biological effects of these radionuclides is emphasized and incorporated into the equivalent dose formalism. The Task Group recommends that a preliminary radiation weighting factor of 10 be used for deterministic effects of Auger electrons, and a value of 20 for stochastic effects.

1. INTRODUCTION

A. Scope

This report is the third of a series presented in *Medical Physics* by the AAPM Nuclear Medicine Task Group No. 6 on Auger-electron-emitting radionuclides.[1] The first report, completed primarily by Sastry, is a review of the physics and radiobiological literature on the most-studied Auger electron emitter ^{125}I.[2] The second report, prepared mainly by Howell, contains complete average radiation spectra for a number of Auger electron emitters (also referred to as Auger emitters) that include the very-low-energy N- and O-shell Auger electrons." These theoretical spectra, calculated using Monte Carlo methods, are necessary for computing the absorbed dose from incorporated Auger emitters. The present report reviews dosimetry of Auger emitters at molecular, cellular, and organ levels, and discusses the merits and shortcomings of each approach with respect to their capacity to predict biologic effect. Hence, this report serves as a guide for dosimetry of internal Auger emitters.

B. The Auger process

In the early 1920s Pierre Auger[4] was investigating electron tracks in a cloud chamber produced by photoelectric interactions of low-energy x rays. He observed that in many instances multiple electron tracks emanated from the same point in the chamber. He concluded that the multiple electron emissions arose from inner shell atomic electron transitions in which the energy gained *(SE)* could, instead of being released as a characteristic photon, be transferred to an orbital electron ejected with an energy $(d\,E) - E_b$, where E_b is the binding energy of the ejected electron. This nonradiative transition process, which competes with radiative transitions (characteristic x-ray emission), has been called the Auger effect in honor of its discoverer. The probability of emission of a characteristic x ray is given by the fluorescence yield (ω). The probability of an Auger transition is then given by l-o. Since the work of Pierre Auger, nonradiative transitions have been classified into three categories: Auger, Coster-Kronig, and super-Coster-Kronig transitions.[5] These three types of nonradiative processes are discussed in detail by Sastry[2] in the first report of this Task Group. For the sake of simplicity, the electrons emitted in these nonradiative transitions are generally called Auger electrons.

C. Auger-electron-emitting radionuclides

Auger electrons are emitted by about one-half of the known radionuclides (radionuclides that decay by electron capture or internal conversion). Both these decay processes result in the creation of a vacancy in an inner atomic she11.[2,6] The filling of this vacancy produces a cascade of inner shell electron transitions with the emission of numerous Auger electrons. Such radionuclides, which are referred to as Auger emitters, are widely used in nuclear medicine (e.g., ^{67}Ga, ^{99m}Tc, ^{111}In, ^{123}I, ^{125}I, and ^{201}Tl).

The significance of Auger electrons in the dosimetry of internal emitters remained neglected for a number of years, largely because the energy deposited in tissue by Auger electrons is usually negligible compared to the total energy released in the decay of the radionuclide. However, the impor-

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tance of these electrons did not go unnoticed in nuclear chemistry.[7-9] Carlson and White in the early 1960s performed a number of experiments in which they investigated the atomic charge spectra following the decay of ^{125}I in radiolabeled methyl and ethyl iodide.[7] These studies demonstrated that a large number of nonradiative transitions follow the creation of a vacancy in the inner atomic shell, and since each positive charge on the residual atom is the consequence of an electron emission, anywhere from 1-20 Auger electrons must be emitted per K- or L-shell vacancy with an average of about 7-10. The energies of these electrons depend on the atomic binding energies of the atom. The most energetic Auger electrons result from transitions to the K-shell (25-27 keV), but most of the electrons are produced by transitions between the outer orbitals and therefore have energies <500 eV, with corresponding ranges of <25 nm in unit-density matter.[3]

These early experiments of Carlson and White[7] raised questions regarding the biological effects of Auger cascades when the Auger emitter was localized on critical molecular structures in the cell. At about the same time, Wrenn[10,11] recognized the role of Auger electrons in internal radionuclide dosimetry. These initial studies were subsequently followed by numerous radiobiological investigations that examined the effects of incorporated Auger emitters at the molecular, cellular, and organ levels. These studies and their implications were reviewed in detail by Sastry in the first report of this Task Group;[2] however, for pedagogical purposes, the salient features will be briefly mentioned. Experimental studies with oligodeoxynucleotides have shown that the range of damage imparted by Auger cascades in isolated molecules is only over a few base pairs.[12,13] Cellular and organ studies have demonstrated that when Auger emitters are introduced into the cytoplasm of cells, the effects are typical of those caused by radiations of low-linear-energy transfer (LET).[14-21] In contrast, when Auger emitters are incorporated into the DNA of cells, the resulting survival curves are similar to those for high-LET alpha particles.[18-20,22-33] Finally, recent *in vivo* studies with radioprotectors show that the intense local damage imparted by Auger cascades can be mitigated despite the fact that they impart high-LET-type effects.[18,34-39]

D. Dosimetry of Auger emitters

The various *in vitro* and *in vivo* radiobiological studies with Auger emitters have led to the following conclusions: (1) The radiological risk associated with internal exposure to Auger electron emitters may have been underestimated, and therefore may require reappraisal.[31,32,40-45] (2) Auger electron emitters may serve as precision radiobiological tools to elucidate the primary radiosensitive targets in the cell.[18,21,29,46-48] (3) Radiolabeled compounds that target DNA may be useful for cancer therapy when Auger emitters are employed.[49-57]

Dosimetry plays a key role in the radiobiology of Auger emitters whether attempting to understand the basic mechanisms of molecular damage imparted by Auger cascades, or predicting their effects at the cellular or organ level. Accordingly, dosimetry at all of these levels can be important. The following sections describe dosimetry techniques at the DNA, cellular, and organ level, and discuss their merits and limitations.

II. INGREDIENTS OF DOSIMETRIC CALCULATIONS

Accurate dosimetric calculations are essential for interpreting radiobiological experiments with Auger emitters. The ingredients of any dose calculation, regardless of the spatial dimensions of the target region, are

(a) radiation spectra of the radionuclide,
(b) energy loss characteristics of the emitted radiations, and
(c) biological uptake and clearance patterns of the radiochemical.

The physical half-life of the radionuclide, characteristics of the emitted radiations, and interaction properties of the radiations with matter are the physical information required for dosimetry calculations, whereas the biological information required is the biokinetics data. These aspects are discussed below.

A. Radiation spectra

Traditionally, the radiation spectra provided by the ICRP[58] and the MIRD Committee"' have been used for dosimetry of internal emitters. Although the radiation spectra provided in these tables for radionuclides that decay by alpha and beta modes is usually adequate, the data for radionuclides that decay by electron capture (EC) and internal conversion (IC) (i.e., Auger emitters) are sometimes inadequate for radiation dosimetry. For Auger emitters, the very-low-energy N- and O-shell electrons which comprise the bulk of the electron emission for high Z elements have been ignored in the ICRP and MIRD spectra. Although relatively unimportant when calculating the dose to large volumes, the local energy deposited by these extremely short-range (several nanometers) electrons is very important when calculating the dose delivered to small volumes (i.e., less than 1 μm in diameter).[3] Hence, more detailed spectra are required for Auger electron dosimetry.

The Auger electron spectra of radionuclides are discrete, reflecting the energies of orbital transitions within the atom. Thus, only a finite number of electron energies are possible, which may number only a few for atoms of very low atomic number, to hundreds for high Z elements. Since the atomic de-excitation following the creation of an inner atomic shell vacancy is a highly stochastic process, the permutations of individual electron spectra resulting from Auger cascades in high Z atoms can number many thousand.[60] Furthermore, the number of permutations can be even larger for radionuclides that undergo more than one Auger cascade per disintegration. For example, ^{125}I decays by electron capture followed by internal conversion, and ^{193m}Pt decays by three successive internal conversion processes.[61] Hence, complete Auger electron spectra are extremely complex.

Detailed Auger electron spectra have been calculated by a number of groups using either Monte Carlo[52,60,62,63] [J. L. Humm, "The analysis of Auger electrons released following

the decay of radioisotopes and photoelectric interactions and their contribution to energy deposition," Ph.D. thesis (Polytechnic of the South Bank, London, 1983). This will be referred to hereafter as JLH thesis.] or phenomenological techniques.[6] A number of assumptions are made in calculating the spectra that are described in Report No. 2 of this Task Group[3] and will only be briefly outlined here. First, the electron transition probability data used are for atoms containing only a single inner shell vacancy (frozen orbital approximation). As the electron cascade in the atom progresses, the number of vacancies rapidly increases, and the effect of multiple vacancy configurations on the transition rates is not known. Whereas the calculated yields and energies of the higher-energy Auger electrons agree well with experimental data, data on the very-low-energy electrons are limited. The second major assumption concerns the calculation of Auger electron energies. With the exception of the spectra of Pomplun *et al.*,[62] all the Auger spectra calculations have used the $Z/Z+1$ approximation of Chung and Jenkins.[64] Pomplun[62] has used the quantum mechanical computer code of Desclaux[65] to obtain binding energies for atoms with multiple inner shell vacancy configurations. This approach results in an exact energy balance between the nuclear transition energy and the total energy carried by the emitted electrons, photons and potential energy of the atom. However, it should be pointed out that the same frozen orbital approximation was used for the transition rates in these calculations. Since this calculational method dynamically calculates the binding energies, it may result in a more accurate estimation of the Auger electron energies. It should be noted that the binding energies of the outer orbitals involved in Coster-Kronig transitions may be quite different when the Auger emitter is bound. to a large molecular structure in a biological system. Hence, this method may not offer any overall increase in the accuracy of dose calculations. The third major assumption concerns the issue of charge neutralization in the condensed phase. Again, with the exception of Pomplun *et al.* ,[62] all calculations of this type have assumed that vacancies created in the valence shell are immediately filled by electrons from the continuum (fast neutralization). Not making this assumption sharply reduces the calculated number of Auger electrons emitted, and results in a residual ionization potential on the atom, the energy of which must be locally deposited over some unknown spatial dimensions. Recent experiments by Rao and co-workers[18,34-39] on radioprotection against Auger cascades from DNA bound ^{125}I indicate that the indirect action of radical species plays a major role in causing damage to the radiosensitive targets, thereby suggesting a limited role for charge neutralization in the Auger effect in the condensed phase.

With the above considerations in mind, a consistent set of average Auger electron spectra were calculated and presented in Report No. 2 of this Task Group[3] for a number of radionuclides using a combination of the assumptions and techniques used by Charlton and Booz,[60] Sastry *et al.*,[6] Humm *et al.*,[66] and Howell *et al.*[52]

B. Energy loss by Auger electrons

A variety of techniques have been employed for determining the energy deposited in target regions by low-energy Auger electrons. For dimensions ranging from nanometers to micrometers, Sastry *et al.*[6,67] and Howell *et al.*[31,68] used the electron range-energy relationship for unit-density matter of Cole[69] which is based on a fit to experimental data for electron energies ranging from 20 eV to 2 MeV:

$$E(R) = 5.9\,(R + 0.007)^{0.565} + 0.00413\,R^{1.33} - 0.367, \quad (1)$$

where E is electron energy in keV and R the electron range in micrometers in unit-density matter. Differentiation of this equation results in the following stopping power relationship for electrons:

$$\frac{dE}{dR} = 3.33(R+0.007)^{-0.435} + 0.0055R^{0.33}. \quad (2)$$

Howell *et al.*[70] have noted that the fit is poor for energies less than 0.4 keV. Therefore, for electrons of energies 0.06-0.4 keV, a separate fit to the experimental data was employed:

$$\frac{dE}{dR} = 29.5 - 666.67R. \quad (3a)$$

For electrons of energies <0.06 keV, the following fit was used

$$\frac{dE}{dR} = a + bR + cR^2 + dR^3 + eR^4, \quad (3b)$$

where $a = 10.5$, $b = 1.126\text{x}10^3$, $c = -9.251\text{x}10^5$, $d = 2.593\text{X}10^8$, and $e = 4.964\text{X}10^{10}$. These expressions may be appropriately used to obtain absorbed doses to various target volumes containing electron emitting sources (see Sec. III).

Other methods to calculate electron energy loss in matter have been used for dosimetry of incorporated radionuclides. Makrigiorgos[71] used the restricted dose mean LET with a cutoff energy of 100 eV to describe the energy loss as a function of distance. Berger's[72,73] dimensionless scaled point kernel is useful for electrons down to 0.5 keV. However, as discussed earlier, most of the electrons emitted in the Auger process have energies below 500 eV, and thus are below the range of validity of Berger's point kernel tables. Booz *et al.*[74] have provided an extrapolation of Berger's data using a third,-order polynomial fit. This fit allows calculation of the energy absorbed in small volumes from low-energy electrons. Both the above methods provide estimates of the average energy deposition in small target volumes.

An alternative approach for obtaining energy deposition information for Auger electrons is to use Monte Carlo track-structure calculations which model the entire stochastic process of electron interactions with matter. There are currently several electron track-structure codes which follow electron slowing down processes to energies of 10 eV and below, including those of Paretzke,[75] Terrissol *et al.*,[76] Zaider *et al.*,[77] and Wright *et al.*[78] These Monte Carlo electron track-structure simulation codes enable the user to monitor the spatial coordinates of each interaction, together with the

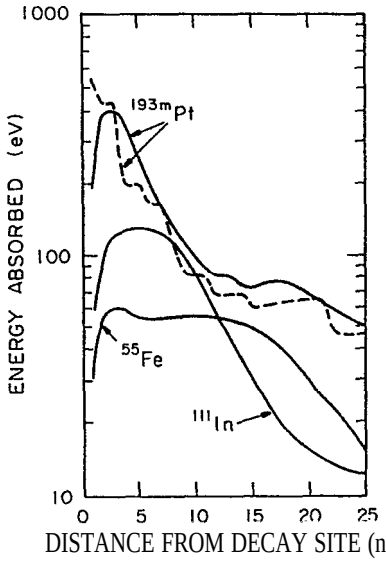

FIG. 1. Localized energy deposition as a function of distance from the decay site for different Auger emitters (Ref. 67). The solid lines are results obtained with the OREC Monte Carlo track-structure code which simulates electron tracks in liquid water (Ref. 78). The dashed line was obtained using Cole's experimental range-energy relationship for unit-density matter given by Eq. (2). The agreement between these two calculations is good except at distances very close to the decay site (<2 nm).

energy deposited at that coordinate. By simulating a statistically significant number (1000-100 000) of electron tracks through the target volume, the mean and statistical distribution of energy deposition within the target volume can be evaluated. However, the more practical energy loss expression [Eq. (2)] of Cole[69] has been shown by Sastry *et al*[67] to provide a reasonably accurate estimate of the average energy deposited by Auger emitters even down to nanometer volumes (Fig. 1).

C. Uptake and retention of radionuclide

The dose to a biological target depends in part on the cumulated activity in the target and its surroundings. The extreme short range of Auger electrons may require data on the spatial localization of the emitters relative to the targets with micron and perhaps Angstrom resolution. However, such information cannot readily be obtained from patient, animal, or cell culture studies, although it is possible to obtain radiopharmaceutical distribution at the cellular and multicellular levels using cell separation and autoradiographic techniques.[18,55,63,79-84] Presently, little is known about the kinetics and distribution at the cellular and subcellular levels for most Auger-electron-emitting radiopharmaceuticals; however, some information is available for a limited number of them. This information plays a critical role in the dosimetry of Auger emitters, and therefore is necessary for predicting the biological effects caused by this class of radionuclides.

III. DOSIMETRY

Dosimetry is an essential component in understanding the radiotoxicity of Auger-electron-emitting radionuclides. However, the highly localized energy deposition in the immediate vicinity of the decay site raises a question as to how the absorbed dose should be calculated for Auger electron emitters. The answer to this question depends on a variety of factors which are outlined below.

(1) How important are the differences in the various calculated Auger electron spectra? Do discrepancies in the yields of very-low-energy electrons between 20-100 eV have implications for the local energy deposition and consequently upon dose response relationships for radiobiological effects?
(2) Can the relationship between absorbed dose and the radiotoxicity of internal Auger emitters be adequately evaluated using average Auger electron spectra, or does one need to fold in the full stochastics of atomic deexcitation into the calculations?
(3) Is fast neutralization of the vacancies in the valence shell taking place during the Auger cascade process? If not, is the absorbed dose calculated using complete radiation spectra sufficient to predict radiation toxicity, or should charge buildup and neutralization effects be considered as well? If so, how should local energy deposition from the residual ionization potential be considered in the absorbed dose calculation?

The answers to the above questions depend somewhat upon the choice of the biological system and target volume. Ideally, the biological targets are the primary radiosensitive sites, which are presumably located in the cell nucleus. However, the location and size of these sites is not well known. Furthermore, the position of the radionuclides relative to these sites must be known in order to calculate the absorbed dose to the critical targets.[18,19,46-48,85] In the absence of this information, the absorbed dose from Auger emitters must be calculated at a level suited to the biological system employed. Hence, a number of target volumes are of interest:

(1) individual strands or bases of the DNA molecule,
(2) supercoiled DNA,
(3) cell or cell nucleus,
(4) bulk tissue.

Choosing the target volume, however, is complex. The radiation properties of the radionuclide certainly play a role in this regard. Just as important is the distribution of the radioactivity within the cells, which in turn depends on the chemical nature of the radiocompound. Hence, the appropriate target volume must be determined on a case-by-case basis. For example, Rao and colleagues[18,20,86] have shown that the lethal effects caused by *cytoplasmically* localized Auger emitters can usually be adequately predicted using conventional organ dosimetry. In contrast, organ dosimetry may not be at all useful in predicting DNA strand breaks. The remainder of this report will be devoted to the dosimetry of Auger emitters at a variety of spatial levels including DNA, cellular, multicellular, and organ levels.

A. DNA dosimetry

It is now well recognized that Auger emitters exhibit high LET-type radiotoxicity only when the radionuclide is in close

proximity to the DNA. Accordingly, there has been substantial interest in the dosimetry of Auger electrons at the DNA level.[6,78,87-94] Charlton[89] and Charlton and Humm[87,90] constructed a simple model of the DNA duplex for the purpose of energy deposition calculations. The geometric model of the DNA molecule was assumed to be a solid cylinder of diameter 2.3 nm representing the outside of the double helix. The cylinder consisted of a series of discs of 0.34-nm thickness, corresponding to the base separation along the strands. The DNA was assumed to be of unit-density throughout. This simplistic model of the DNA molecule enables approximate calculations of the energy deposition within the DNA arising from Auger cascades. To this end, the MOCA7B code of Paretzke[75] was employed to simulate electron track interactions in water vapor. One thousand individual Auger spectra, calculated by the method of Charlton and Booz,[60] were generated and fed into the MOCA7B code. A decay site within the DNA molecule was chosen for ^{125}I 0.15 nm from the DNA axis. An individual electron spectrum was picked from the data set of Auger electron spectra, each electron path simulated, and the interaction points and deposited energy determined. The interaction was ignored if it occurred outside the cylindrical DNA volume, whereas within the DNA volume, the exact location relative to the base and strand segments was determined. These data were stored on a per decay basis, and the entire process repeated for 10 000 source decays. This method yields an entire data base of energy deposition events within the DNA volume for Auger-electron-emitting radionuclides.

Of prime interest is the mean energy deposition in the DNA as a function of the location of the decay site relative to the DNA axis. Figure 2 displays a rapid decrease of the mean energy deposition ε in the DNA target volume as the distance of the ‘“I atom from the DNA axis increases. Results are presented for the ^{125}I Auger electron spectra calculated by Pomplun,[62] Charlton and Booz,[60] and the spectrum of Howell in AAPM Report No. 2 of this Task Group.” Energy deposition data are not shown for conventional ICRP[58] and MIRD[59] ^{125}I radiation spectra because these have already been shown to be inadequate for dosimetry in small volumes (<l μ m in diameter).[3] The mean energy deposition to the DNA cylinder calculated using the Pomplun ^{125}I spectrum is approximately 40% lower than that calculated using the Charlton and Booz[60] spectrum for an isolated atom (no charge neutralization) located in the center of the DNA cylinder. The Auger cascade process in an isolated atom results in a charge buildup and consequently the residual daughter has some potential energy (on average 1.07 keV per ^{125}I disintegration). The biologic consequence of such potential energy is not known. For the condensed phase, which is perhaps of greater relevance to radiobiology, Charlton and Booz[60] and Howell[3] have assumed fast charge neutralization[3] so that the residual atom is neutral following the Auger cascade. Here the differences in energy deposition are smaller, yet significant. The primary difference between these two spectra is the inclusion of very-low-energy *O* -shell Coster-Kronig electrons in the latter. Although these electrons appear to be important in terms of localized energy deposition (Fig. 2), theoretical predictions of double-strand breaks are similar for both spectra in the case of ^{125}I (see discussion below, and Table I).

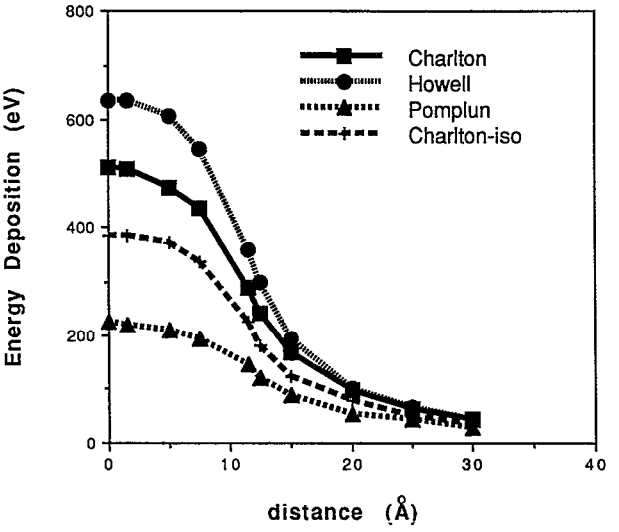

FIG. 2. Mean energy deposited by an ^{125}I decay within a representative DNA cylinder of radius 1.15 nm. The ^{125}I decay occurs at different distances from the central axis of the DNA molecule. Distances greater than 1.15 nm represent decay sites outside of the DNA. The method of calculation is that described by Charlton and Humm (Ref. 87). The data presented arc the mean for 1000 individual ^{125}I Auger electron spectra from Charlton and Booz (with -- ■ --and without --+-- charge neutralization) (Ref. 60). Howell (with charge neutralization) (Ref. 3). and Pomplun (without charge neutralization) (Ref. 62). Note that for decay sites outside the DNA cylinder, there is close agreement between the different Auger electron spectra, since most of the energy deposition results from the higher-energy Auger electrons (*K*-, *L*-, and *M* -shell) where there is good agreement between the spectra. For decay sites within the DNA, there are large discrepancies because of the significant variation in the yield of N- and O-shell Coster-Kronig electrons between the different spectra. However, the reader should note that the differences in energy deposition in the DNA do not result in large differences in DNA strand break yields because energies greater than 17.5 eV are required for strand breakage and many of the very-low-energy O-shell electrons have energies lower than the threshold (see Table I).

For the same average energy deposition within the cell nucleus, the mean energy deposition in the DNA can vary by more than an order of magnitude. The wide stochastic variation in energy deposition to the whole DNA molecule and individual base and strand segments is not shown in Fig. 2. If

TABLE I. Calculated double-strand break yields using the DNA model of Charlton and Humm (Ref. 87), and the Auger electron spectra of Pomplun (Ref. 62), Howell (Ref. 3), and Charlton and Booz (Ref. 60). Data are given per ^{125}I decay at the center of the DNA molecule (0 Å) and on the strand at radius 11.5 Å. The spectrum of Pomplun was for an isolated ^{125}I atom (no charge neutralization) whereas Howell’s was for the condensed phase (fast charge neutralization). Both types of spectra of Charlton and Booz were considered. Note that the differences in double-strand break yields are significantly smaller than the differences in mean energy deposition in the DNA (see Fig. 2).

	Double-strand break yield per 100 ^{125}I decays			
Distance (Å)	Pomplun (isolated)	Charlton and Booz (isolated)	Charlton and Booz (condensed)	Howell (condensed)
0	60.9	61.3	87.7	92.5
11.5	47.5	39.2	67.7	75.1

cell inactivation is related to DNA double-strand breakage, which is in turn related to energy deposition in the individual strand segments, then the analysis of local energy deposition along the DNA strands may be a necessary step to a comprehensive understanding of the relative efficacy of different Auger-electron-emitting radionuclides. It is of interest to note that the stochastic variations in the dose to the DNA is due not only to variations in the radiation spectra of individual Auger cascades, but also due to fluctuations in energy loss along the Monte Carlo simulated electron tracks.

Dose calculations in general, and particularly those at the DNA level, raise the question of their validity with respect to predicting biological response. Experimental measurement of the energy deposited along a DNA strand is not presently feasible. Charlton and Humm[87] have therefore attempted to correlate their energy deposition calculations with the experimental data of Martin and Haseltine,[12] who measured the relative yield of strand breaks as a function of base pair distance from the site of an ^{125}I decay. Charlton and Humm[87] attempted to determine a threshold energy for the production of a single-strand DNA break, such that the distribution of calculated strand breaks as a function of the distance from the ^{125}I decay site matched the experimentally measured data. Close agreement between theory and experiment could be obtained if the threshold energy for DNA strand break production was assumed to lie between 17.5-22.5 eV.[90] These calculations also suggested that "'I decays are likely to produce multiple strand breaks within a distance of ten base pairs of the decay site. In view of the close match between experiment and calculations, this model may also be used to ascertain the relative importance of differences in the various Auger electron spectra discussed above (e.g., Pomplun, Charlton and Booz, and Howell) with regard to predicting biological effects of Auger electron emitters at the DNA level. Table I gives the double-strand break (dsb) yields per 100 ^{125}I decays when the atom is located either at the center or surface of the DNA cylinder. As pointed out above, the differences in dsb yields (Table I) are substantially smaller than the differences in energy deposition shown in Fig. 2. The assumption of fast charge neutralization (as opposed to no charge neutralization) is of substantial importance in predicting double-strand breaks. However, when charge neutralization is assumed, the source of the Auger electron spectrum (i.e., Howell vs Charlton and Booz) does not have a major impact in terms of predicting DNA dsbs caused by the Auger emitter ^{125}I.

Wright *et al.* [78] have performed Auger electron transport calculations in liquid water using the OREC Monte Carlo Code. This computer code simulates direct interaction of the radiations with DNA, and the indirect interactions of the radical species with the DNA. In addition, it evaluates the identity of each chemically reactive species, and simulates the diffusive motion and interaction of these radicals up to 10^{-6}s after the decay. The cylindrical DNA model is 2 nm in diameter and contains 20 reactive sites per 3.4-nm turn of the double helix. The advantage of this method is that it considers both direct radiation energy losses in the DNA, as well as indirect interactions of the radical species with the sensitive sites on the DNA molecule. Wright *et al.* [78] have presented data on the number of direct and indirect DNA interactions resulting from the Auger electron emitters: ^{125}I, ^{195m}Pt, ^{193m}Pt, ^{111}In, and ^{55}Fe, decaying at varying distances from the center of the DNA. For an ^{125}I decay on the surface of the DNA cylinder, they report an average of 21 direct and 44 indirect interactions. The number of indirect DNA interactions for all of the Auger emitters is approximately twice the number of direct DNA interactions. Further data for a 5.3-MeV alpha particle, emitted isotropically from the surface of the DNA cylinder, shows on average only 4 direct and 18 indirect interactions per alpha particle emitted. These calculations suggest that Auger emitters that decay inside or on the surface of the DNA molecule appear, on a per decay basis, to produce more interactions with the DNA than alpha emitters.

A more detailed model of the DNA was developed by Pomplun.[92] In this work, Pomplun uses the available data in the literature on the atomic structure of the DNA. By representing the space occupied by each individual atom by its van der Waals radius, and overlaying the Auger electron track-structure generated by the MOCA8 code of Paretzke,[75] Pomplun obtains the energy deposited on an atom-by-atom basis. The volume within the DNA not occupied by DNA bases or the DNA backbone is assumed to be filled by water. Energy depositions within the van der Waals radii of atoms composing the DNA molecule are assumed to be direct interactions, and those within the areas of water within and around the DNA molecule are assumed to be indirect interactions. The contribution of each interaction to strand break production is evaluated on the basis of a 10-eV threshold energy deposition to produce a strand break. The contribution of direct hits and indirect hits to DNA double-strand break (dsb) induction, from ^{125}I decays occurring in the DNA, are 0.36 dsb/decay and 0.43 dsb/decay, respectively. Pomplun also considers the induction of dsbs from the combination of direct and indirect effects on opposing strands (within 20 base pairs), which amounts to 0.15 dsb/decay. The total number of dsb per ^{125}I decay amounts to 0.94. This model was later improved upon by raising the threshold energy to 18 eV and including the effects of radical species produced,'" thereby yielding a total of 0.6 dsb per ^{125}I decay. This value is in agreement with experimental results for human diploid cells.[93]

The above considerations suggest that the indirect effects of radical species play an important role in the DNA damage caused by Auger cascades. These calculations support the recent series of experiments by Rao and colleagues [18,34,36-39] which show that antioxidants and other chemical radioprotectors substantially mitigate the biological damage caused by DNA-incorporated ^{125}I.

B. Cellular dosimetry

Although DNA-level dosimetry may be useful for providing some understanding of the experimental dsb data available on Auger emitters, in cellular systems one cannot predict the biological outcome with any certainty on the basis of calculations for a single decay site of an Auger emitter on the DNA. This is because numerous radionuclide decays per cell are required to observe any biological effects at the cellular

level (e.g., survival, mutations, transformations, etc.). Therefore, under these circumstances, it is necessary to correlate the biological effect with the absorbed dose to the cell nucleus wherein the radiosensitive targets presumably lie.

In 1966, Wrenn[10] recognized the significance of cellular dosimetry for Auger emitters and calculated the absorbed dose to red blood cells from incorporated ^{55}Fe. The subcellular distribution of the radionuclide (e.g., cell surface, cytoplasm, nucleus) strongly influences the radiotoxicity of Auger emitting radionuclides.[14,17,63] Hence, cellular dosimetry must take the subcellular distribution of the activity into consideration. Such calculations require experimentally determined subcellular distribution which depends on the chemical nature of the radiocompound. Accordingly, more sophisticated methods for cellular dosimetry have evolved over the years to calculate the dose to the cell nucleus.

Humm (Ref. 66 and JLII thesis) calculated energy depositions to spherical volumes of various sizes uniformly filled with Auger emitters using the scaled point kernel data for monoenergetic electrons of Berger.[72,73] Berger provides tabulated data for energy losses by electrons of energies from 0.5 keV to 10 MeV for site diameters from 2-14, μ m. The absorbed fraction ø of emitted energy E_0, absorbed in a sphere of diameter d is given by the integral of the point kernel between 0 and d, multiplied by the geometric reduction factor[95] for a source randomly distributed in a sphere. Mathematically,

$$\frac{\varepsilon}{E_0(d,E_0)} = \frac{1}{r}\int_0^d \left[1 - \frac{3r}{2d} + \frac{r^3}{2d}\right] F\left(\frac{r}{r_0}, E_0\right) dr, \qquad (4)$$

where $F(rlr_o,E_o)$ is Berger's scaled point kernel, giving the fraction of energy absorbed within a spherical shell $4\pi r^2 dr$ at radius r from the source, and the term in square brackets is the geometric reduction factor for a source randomly distributed within a sphere.

As discussed earlier, most of the electrons emitted in the Auger process have energies below 500 eV, and thus are below the range of validity of the Berger point kernel tables. Booz *et al.*[74] have provided an extrapolation of the Berger data using a third-order polynomial fit. This fit allows calculation of the energy absorbed in small volumes from low-energy electrons. The mean energy deposited per decay in the cell nucleus from radioactivity distributed uniformly in the nucleus, for a range of typical nuclear diameters, was given by Humm (JLH thesis) for ^{125}I, ^{125}I, and ^{55}Fe. Values of the mean energy deposited within a 10-μm-diam sphere of unit density for a single decay are given in Table II. For the sake of comparison of different dosimetry techniques, energy deposition in 10-μm spheres was also calculated using the Auger electron spectra presented in AAPM Nuclear Medicine Task Group No. 6, Report No. 2,[3] and absorbed fractions obtained with Eqs. (2) and (5):[68,96]

$$\phi_i = \int_0^\infty \psi(x)\, \frac{1}{E_i}\, \frac{dE}{dX}\bigg|_{X(E_i)-x} dx, \qquad (5)$$

where y is the same geometric reduction factor used in Eq. (4). These results are also presented in Table II. It should be noted that the calculations of Humm employed a different Auger electron spectrum. However, the second report of this Task Group[3] shows that the Auger spectra employed does not play an important role when doses are calculated in volumes with diameters greater than 1 μm. Considering that spectral differences play no role in the total energy deposited in 10-μm spheres from incorporated Auger emitters, it is apparent that the differences in the dosimetry techniques are of no consequence (Table II).

TABLE II. Calculated energy deposited in 10-μm diam. spheres containing some Auger emitters uniformly distributed within.

Radionuclide	Total particle energy emitted (keV) Humm[a]	Energy absorbed (keV) Humm[a]	Total particle energy emitted (kev) Howell[b]	Energy absorbed (keV) Goddu *et al.*[c]
^{125}I	19.9	11.9	19.5	11.5
^{123}I	28.4	5.2	27.6	5.1
^{55}Fe	4.04	3.8	4.18	3.9

[a]J. L. Humm, "The analysis of Auger electrons released following the decay of radioisotopes and photoelectric interactions and their contribution to energy deposition." Ph.D. thesis (Polytechnic of the South Bank, London, 1983).
[b]Reference 3.
[c]Reference 96.

A model to estimate the dose to the cell nucleus from Auger-electron-emitting radiopharmaceuticals was also developed by Sastry and co-workers."*'" This model assumes that the cell and cell nucleus are concentric spheres of unit-density matter. The Auger emitter was distributed uniformly in either the cytoplasm or nucleus of the cell, and the energy deposited in the cell nucleus was calculated using Cole's[69] energy-loss expression for electrons [Eq. (2)]. This method was further simplified to reduce computational times and to accommodate activity distributed on the surface of the cell.[68] Using this approach, Goddu *et al.*[96] have provided absorbed fractions for monoenergetic electron sources (0.1 keV to 1 MeV) distributed in the different cell compartments (cell surface, cytoplasm, nucleus) of cells of various dimensions (radii 2-10 μm). For example, Fig. 3 shows the absorbed fractions as a function of electron energy for a cell diameter of 10 μm and nuclear diameters of 4, 6, and 8 μm. These electron-absorbed fractions may be readily used to calculate the absorbed dose to the cell or cell nucleus from any electron emitting radionuclide distributed in different cell compartments. For the sake of convenience, S values (absorbed dose per unit cumulated activity) were also presented for a number of Auger-electron-emitting radionuclides of medical interest (^{51}Cr, ^{67}Ga, ^{99m}Tc, ^{111}In, ^{123}I, ^{125}I, ^{201}Tl, ^{203}Pb), as well as some β and α emitters.[96] A sample of these data is presented in Table III for a typical cell containing different Auger emitters. The S values for various cell sizes may be obtained from Ref. 96.

It should be noted that in order to calculate cellular absorbed doses, one requires knowledge of the distribution and biokinetics of the radionuclide at the cellular level. Although this information is sufficient to calculate cellular absorbed doses, there is substantial experimental evidence *in vitro* to suggest that the absorbed dose to the cell nucleus alone is insufficient to predict the biological effects of Auger electron

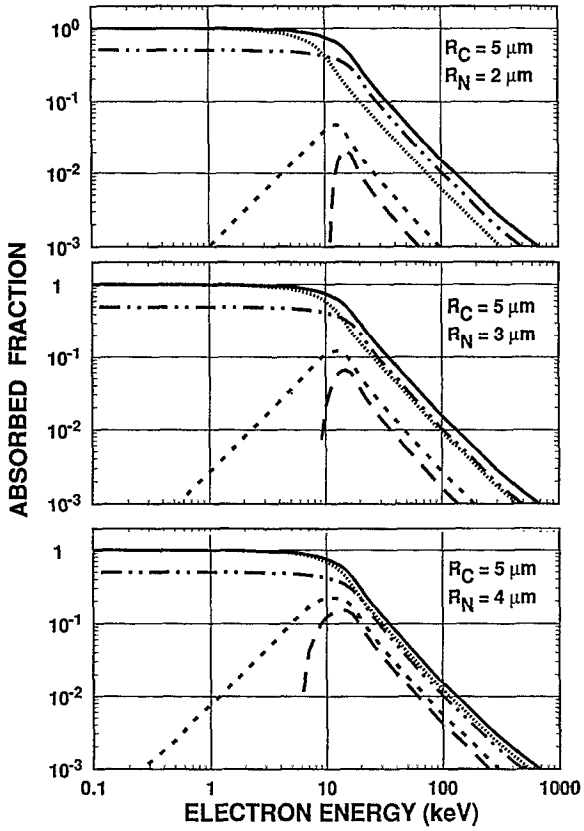

FIG. 3. Absorbed fractions for monoenergetic electron sources distrihutcd uniformly in various compartments of spherical cells of unit-density matter. The radii of the cell (R_C) and cell nucleus (R_N) are indicated. Radioactivity is distributed in the source region (cell surface. cytoplasm, or nucleus) and the fraction of emitted energy deposited in the target region (cell or cell nucleus) is calculated. The target+-source configurations are: cell+-cell (-), cell ← cell surface (--..), nucleus-nucleus (.....), nucleus---cytoplasm (--), nucleus ← cell surface (--).

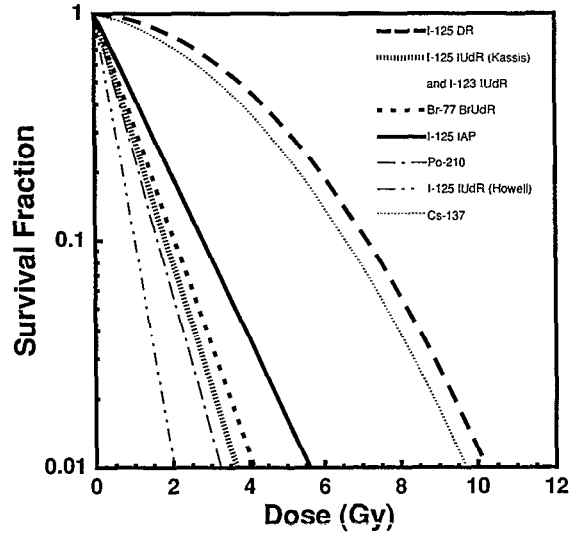

Fig. 4. Dose-response curves for a variety of Auger-electron-emitting radiochemicals incorporated into cultured Chinese hamster V79 cells: ^{125}dihydrorhodamine (I-125 DR) (Ref. 16) ^{125}Iododeoxyuridinc [I-125 IUdR (Kassis)] (Ref. 27), ^{123}Iododeoxyuridine (I-123 IUdR) (Ref. 102), ^{77}Bromodeoxyuridine (Br-77 BrUdR) (Ref. 281, ^{125}Iodoantipyrcne (I-125 IAP) (Ref. 103). ^{210}Po-citrate (Ref. 31), ^{125}Iododcoxyuridinc (I-125 IUdR (Howell)] (Ref. 31), and acute external ^{137}Cs gamma rays (Ref. 31). Note that cytoplasmically localized ^{125}1-DR produces effects akin to low-LET external gamma rays. In contrast, radiochemicals that localize in the cell nucleus and bind to DNA cause high-LET-type effects similar to those caused by 5.3.MeV alpha particles emitted by incorporated ^{210}Po.

emitters localized in the cell nucleus. For example, when the Auger emitter is incorporated into the cytoplasm, and the dose is calculated to the cell nucleus, the dose response curves (Fig. 4) are similar to the curve for external irradiation with ^{137}Cs γ rays.[16] In contrast, localization of the Auger emitter on the DNA yields much greater biological response (Fig. 4) than γ rays per unit dose to the cell nucleus.[17,31] This suggests that the absorbed dose to the cell nucleus alone cannot reliably predict the biological effects of Auger emitters incorporated into cells. This does not mean that the biological effects of such radionuclides cannot be predicted altogether, rather a solid database of dose-response information is required along with dosimetry calculations (see Sec. IV).“”

The above cellular dosimetry approaches are adequate when the dose to the cell nucleus from surrounding tissue (cross-dose) is relatively small compared to the dose to the cell nucleus from decays occurring within the cell itself (self-dose). The self-dose will clearly dominate when Auger emitters are localized in the nucleus of cells. However, when one considers a cluster of cells, there may be instances where the cross-dose may constitute a significant fraction of the total dose to the cell nucleus. This depends on a variety of factors including subcellular distribution of the activity, dimensions of the cell, cell nucleus, and cluster, and the penetrating na-

TABLE III. The S values[96] for some Auger emitters assuming uniform distribution in different compartments of cells 10 μm in diameter with 8-μm nucleus.[a]

Radionuclide	C←C (Gy/Bq·s)	C←CS (Gy/Bq·s)	N←N (Gy/Bq·s)	N←Cy (Gy/Bq·s)	N←CS (Gy/Bq·s)
^{51}Cr	1.06×10^{-3}	5.39×10^{-4}	2.04×10^{-3}	1.44×10^{-4}	2.49×10^{-8}
^{67}Ga	1.86×10^{-3}	9.94×10^{-4}	3.45×10^{-3}	6.32×10^{-4}	2.64×10^{-4}
^{99m}Tc	8.16×10^{-4}	4.23×10^{-4}	1.55×10^{-3}	8.68×10^{-5}	4.76×10^{-5}
^{111}In	1.47×10^{-3}	8.03×10^{-4}	2.70×10^{-3}	3.03×10^{-4}	1.94×10^{-4}
^{123}I	1.56×10^{-3}	8.36×10^{-4}	2.93×10^{-3}	2.72×10^{-4}	1.40×10^{-4}
^{125}I	3.51×10^{-3}	1.86×10^{-3}	6.60×10^{-3}	5.94×10^{-4}	2.62×10^{-4}
^{201}Tl	4.24×10^{-3}	2.29×10^{-3}	7.83×10^{-3}	1.29×10^{-3}	6.91×10^{-4}
^{203}Pb	2.67×10^{-3}	1.40×10^{-3}	5.03×10^{-3}	7.14×10^{-4}	3.21×10^{-4}

[a]The designations for target←source configurations are C—whole cell, Cy—cytoplasm, CS—cell surface, N—cell nucleus.

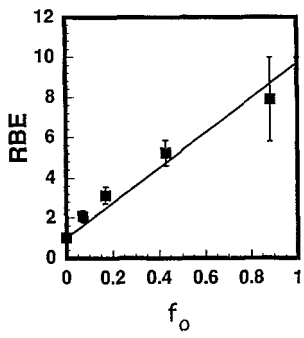

FIG. 5. Dependence of relative biological effectiveness (at 37% survival) of ^{125}I on the fraction of testicular activity that is bound to DNA f_0 in the mouse testis. The RBE is linearly dependent on the fraction that is bound to DNA (RBE=1+8.7 f_0) (Ref. 32).

ture of the conversion and K-shell Auger electrons emitted. These aspects were examined by Sastry *et a1.* [97] and Goddu *et al.* [98] who found that the self-dose clearly dominates when Auger emitters are localized in the nuclei of the cells in the cluster. However, when the radioactivity is distributed on the cell membrane or in the cytoplasm of the cells, the cross-dose can be as important as the self-dose when the cluster size is small (d<400, μm) and most of the cells in the cluster are labeled. Under these labeling conditions, the cross-dose to the nuclei dominates when the cluster size is large (d> 400 μm), suggesting that the mean absorbed dose to the cluster is sometimes adequate for Auger emitters. For those interested in multicellular dosimetry for Auger emitters, the necessary computational tools are provided in Refs. 68, 97, and 98. Such calculations require considerable biological information such as subcellular distribution, localization of the radioactivity in the tissue on a multicellular scale, and the time dependence of such distributions. These aspects are discussed in several recent articles.[79-81]

C. Organ dosimetry

Although dosimetry at the DNA, cellular, and multicellular levels are of substantial interest, it is usually (ascites and blood cells being the exceptions) impractical to consider dose calculations at these levels for *in vivo* applications of Auger emitters. The extensive use of Auger emitters in nuclear medicine calls for more practical dosimetry approaches for these radionuclides. Current *in vivo* quantitation techniques in nuclear medicine usually can provide the necessary data required to calculate mean organ absorbed doses using MIRD procedures.[99] Although mean organ doses calculated in this manner are useful for risk assessment or prediction of biological outcome in most cases, this may not always be the case for Auger emitters. This is evidenced by the data of Rao and co-workers [19,20,86] who, using the mouse testis system, have shown that the biological effects of Auger emitters may not be predicted on the basis of organ doses alone, but are strongly dependent on the subcellular distribution of the radionuclide. Their recent experiments[32] show that biological effects of the prolific Auger emitter ^{125}I depend on the fraction of organ activity that is bound to DNA of the cells (Fig. 5). Hence, knowledge of both the subcellular distribution and the mean organ dose is necessary for predicting the biological effects of Auger electron emitters.

There is *in vivo* evidence that some Auger-electron-emitting radiopharmaceuticals used in nuclear medicine, such as ^{201}TIC1 (Ref. 42) and ^{111}in-oxine (Ref. 63), result in radiotoxicities greater than predicted based on the mean absorbed dose. Therefore, we should remain vigilant, especially regarding the introduction of new radiopharmaceuticals.

IV. DISCUSSION

Whether coming with an interest in radiation biology, radiation protection, or radiation therapy, one may ask how the absorbed dose should be calculated in order to predict the biological effects of Auger emitters. There is no simple answer because of the highly localized energy deposition in the immediate vicinity (~10 nm) of the decay sites of Auger emitters. Although dosimetry may, in principle, be performed at any level (DNA, cell, or organ), the appropriate level is dictated by the biological system and the endpoint, as well as the ability to obtain the necessary biological information from the system that is required to perform dose calculations at the desired level. The appropriateness of the selected dosimetry model can only be substantiated by obtaining consistent dose response relationships. Surprisingly, there is only limited experimental data within a given biological system and endpoint which systematically examines dose-response relationships for a variety of Auger emitters bound to various sites within the cell. Such data are essential for establishing the validity of a given dosimetric model.

A. DNA dosimetry

When Auger emitters are attached to the DNA in the cell nucleus, the energy is not uniformly deposited throughout the cell nucleus, and the dose to the DNA is not equal to the cell nuclear dose. Consequently it may be necessary to calculate the absorbed dose to the DNA in order to construct consistent dose response relationships. Values of the mean energy deposition per decay to DNA resulting from Auger emitters attached to DNA have been published for a few radionuclides.[90] The relationship between the calculated dose and observed biological effects on DNA have so far only been tested for two radionuclides, ^{125}I and ^{123}I. Makrigiorgos *et al.* [100] measured the relative yields of double-strand breaks for ^{125}IUdR and ^{123}IUdR and found them to be in reasonable agreement with the ratio of their mean energy deposited in the DNA, and their predicted strand break yields." Therefore, the mean absorbed dose to the DNA appears to correlate well with double-strand break yields in cultured mammalian cells. Many more such tests are needed to verify the utility of DNA dose calculations to predict the relative efficacy of different Auger emitters in causing strand breaks, and in turn causing cell death. The relationship between strand breaks and cell survival has not been clearly established for Auger emitters.[47,48,100,101] In fact, Hofer *et al.* [47,48] have recently suggested that DNA may not be the appropriate biological target, rather some higher-order structures may be the primary radiosensitive targets that are responsible for cell death. Moreover, induction of cell death by Auger emitters

attached to the DNA requires hundreds of decays per cell nucleus.[23,27,28,31,47,48,101,102] How the interaction of the damage resulting from these numerous decays leads to cell death remains unclear. Even so, it may be possible to use existing radiobiological survival data on the number of radionuclide decays required for cell inactivation (e.g., 37% survival) to establish a relationship between cell survival and the energy deposited in the DNA.

B. Cellular dosimetry

A considerable effort has been expended in correlating cell survival in vitro with the mean absorbed dose to the cell nucleus. The cell nucleus is chosen as the target volume because it is generally believed to contain the primary radiosensitive sites in the cell and its absorbed dose can be readily calculated. In order to calculate the dose to the cell nucleus, due regard must be given to the microscopic localization of the Auger-electron-emitting radiopharmaceutical. When Auger emitters were localized in the cytoplasm of the cell, the dose-response relationship was similar to that observed for acute external photon irradiation (RBE~1) (see Fig. 4). However, when various Auger emitters (^{125}I, ^{125}I, ^{77}Br) were covalently bound to the DNA in the cell nucleus using iodo- and bromodeoxyuridine,[27,28,102] the dose response curves were similar to those obtained for incorporated alpha emitters" with values of relative biological effectiveness (RBE) ranging from 7-9 (Fig. 4). Essentially the same RBE value was obtained for ^{125}iododeoxycytidine, suggesting that thymine and cytosine base sites are equally radiosensitive to Auger cascades." Somewhat lower RBE values (RBE~4) have been obtained when Auger emitters were introduced into the nucleus but not covalently bound to DNA.[17,63,103-105] These results suggest that the mean absorbed dose to the cell nucleus may be used to correlate dose and effect only when a correction factor is introduced that accounts for the subcellular distribution of the radioactivity. Hence, the location of the Auger cascade relative to the DNA in the cell nucleus plays a significant role in the determination of radiotoxicity.

It is interesting to note that experiments in cultured cells[27,28,101,102] with different Auger emitters (^{77}Br, ^{123}I, ^{125}I) covalently bound to DNA as bromo and iododeoxyuridine yielded essentially the same D_{37} (and hence, RBE)[59] despite their very different physical half-lives and Auger electron spectra.[3] These radionuclides emit about 7, 15, and 25 Auger electrons per decay, respectively. When uniformly distributed in the cell nucleus, the radionuclides ^{77}Br, ^{123}I, and ^{125}I deposit about 4.1, 4.7, and 10.9 keV in the cell nucleus per disintegration, respectively [Eq. (5)]. The number of disintegrations required to achieve D_{37} for ^{123}I and 77Br were 2.3 and 3.1 times the number required for ^{125}I,[101] which are similar to the ratios of energy deposited in the nucleus (2.3 and 2.7). Therefore, as pointed out by Kassis *et al.*,[101] there are no saturation effects in terms of imparting biological damage to the DNA. Whether this is true for other Auger emitters and radiochemicals that are noncovalently bound to DNA remains to be explored.

For the practical purpose of determining cell and cell nuclear doses, the differences in various Auger electron spectra discussed above do not result in significant variations (Table II). Therefore, the spectra in Report No. 2 of this Task Group and Eq. (4) or (5) may be used to calculate the absorbed doses at the cellular level.[106] For convenience, Goddu *et al.*[96] have conveniently tabulated *S* values (Gy/Bq s) for a variety of Auger emitters localized in various compartments (cell surface, cytoplasm, nucleus) of cells of different dimensions. With knowledge of the biokinetics and subcellular distribution of the radiochemical, the *S* values can be conveniently used to calculate the absorbed dose to the cell or cell nucleus. In the event that *S* values for the emitter of interest are not provided, absorbed fractions for monoenergetic electrons can be employed in conjunction with the Auger electron spectrum to calculate cellular absorbed doses.[6,96] When the Auger emitter is distributed in a small cluster of cells, the neighboring cells may contribute significantly to the absorbed dose to the cell nucleus. The tools needed to calculate the total dose (self-dose+cross-dose) under these circumstances are available.[97,98] When using the calculated doses to predict biological effects, the increased effectiveness (RBE>1) of intranuclearly localized Auger emitters must be taken into account.

C. Organ dosimetry

There is considerable evidence based on *in vivo* experiments in mouse testis that demonstrates the dependence of the radiotoxicity of Auger emitters on their subcellular distribution[18,20,30,32,63,86,107] More specifically, when Auger emitters are situated outside the cell or in the cytoplasm, RBE values of about 1 for spermatogonial cell survival are ohtained when the mean organ dose is used to calculate the RBE[18-20,86] On the other hand, when ^{125}I is covalently bound to the DNA in the cell nucleus either as iododeoxyuridine or iododeoxycytidine, RBE values of about 7-8 are obtained." These RBE values are similar to those obtained in the same experimental system for high-LET alpha particles emitted by incorporated ^{210}Po, ^{212}Bi, and ^{212}Po.[30,108] Interestingly, similar RBE values for DNA-bound ^{125}I and ^{210}Po are observed in vitro." When spermhead abnormalities are taken as the biological endpoint, the RBE values for Auger emitters are substantially higher than those for cell survival.[86] Depending on the subcellular distribution of the radiochemical, RBE values for induction of spermhead abnormalities range from 2-60. Furthermore, there is a linear correlation between the RBE for induction of abnormalities and the RBE for cell survival (Fig. 6).[86] It is well recognized that the RBE for inducing stochastic effects (e.g., mutations, cancer induction) differs significantly from those for deterministic effects (e.g., cell survival).[109] This dependence on the biological endpoint is reflected in the survival (deterministic) and abnormal (stochastic) results obtained in the same experimental system.

D. Equivalent dose for Auger electron emitters

In view of the high RBE values observed for Auger emitters both *in vivo* and in vitro, and considering that most radiopharmaceuticals used in nuclear medicine are Auger electron emitters, the radiological safety of these radionuclides

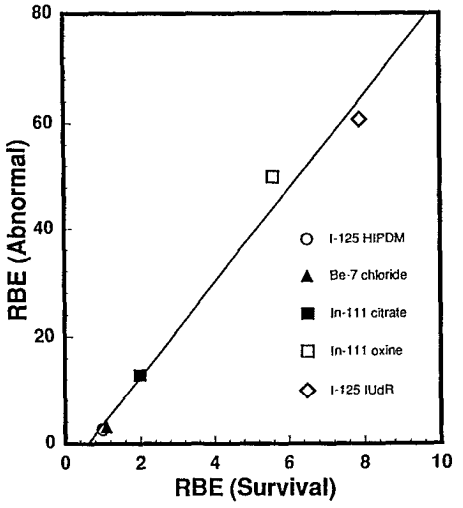

FIG. 6. Correlation of spermatogonial cell killing and induction of sperm-shape abnormalities in mouse testis with incorporated radionuclides (Ref. 86). For all of the radiochemicals, the values of relative biological effectivetress (RBE) were obtained by comparing their effects with those of acute 120-kVp x rays. A linear relationship is observed between the two experimental endpoints (Ref. 86).

needs to be addressed.[32,43] Ideally, a weighting factor should be ascribed to each Auger-emitting radiochemical based on the observed relative biological effectiveness of the agent. This would be a monumental task considering the large variety of radiochemicals used in biomedical research and nuclear medicine. One way to simplify the task is to separately account for the RBE values of the Auger electrons and all other radiations. The RBE for Auger electrons of course depends on the subcellular distribution, i.e., intranuclear DNA appended, intranuclear non-DNA appended, cytoplasm, and extracellular. In this way, the risk associated with any new radiopharmaceutical could be estimated from a study of the subcellular distribution of the radiopharmaceutical. In this context, the recent experiments of Howell *et al.* [32] using the mouse testis system are of interest. Using mixtures of H^{125} IPDM which localizes in the cytoplasm, and ^{125}IUdR which binds to DNA in cell nucleus, the fraction of organ activity that was bound to the DNA of the testicular cells was varied. The resulting RBE values for cell survival were linearly related to the DNA-bound fraction of the organ activity f_0 (Fig. 5) according to the relationship RBE=1.0+8.7f0. This suggests that the equivalent dose for Auger emitters may have a similar dependence.'"

Following the formalism of the ICRP,[110] the equivalent dose in an organ or tissue T is defined as $H_T = w_R D_{T,R}$, where w_R is the radiation weighting factor for stochastic effects and $D_{T,R}$ is the mean absorbed dose from radiation R. For mixed radiations, such as those emitted by many radionuclides including Auger emitters,

$$H_T = \sum_R w_R \cdot D_{T,R}. \tag{6}$$

Therefore, when all of the organ activity is incorporated into DNA, the equivalent dose for Auger emitters may be written as[32]

$$H_T = H_{T,R_{\text{Auger}}} + H_{T,\text{other}} = w_{R_{\text{Auger}}} \sum_{R_{\text{Auger}}} D_{T,R_{\text{Auger}}} + \sum_{R_{\text{other}}} w_{R_{\text{other}}} \cdot D_{T,R_{\text{Auger}}}. \tag{7}$$

Further modification of the above equation to accommodate the dependence of $H_{T,R_{\text{Auger}}}$ on the subcellular distribution of Auger emitters is required:

$$H_{T,R_{\text{Auger}}} = [1 + f_0(w_{R_{\text{Auger}}} - 1)] \sum_{R_{\text{Auger}}} D_{T,R_{\text{other}}}, \tag{8}$$

where f_0 is the fraction of organ activity that is bound to DNA. The quantity $W_{R_{\text{Auger}}}$ is the radiation weighting factor for Auger electrons only and does not include any other radiations such as a, b, x, y rays and conversion electrons. Separation of the biological effects of the Auger electrons from other radiations emitted by the radionuclide is not possible experimentally because the observed RBE values are for the composite spectrum of emissions. A method to estimate $W_{R_{\text{Auger}}}$ is discussed in Ref. 32. It should be noted that Eq. (8) is based on experiments where ^{125}I is covalently bound to DNA in the cell nucleus. When the Auger emitter is localized in the nucleus but not covalently bound to DNA, somewhat lower RBE values may be expected as discussed above and therefore the expression for $H_{T.R_{\text{Auger}}}$ must be modified accordingly." However, there is presently insufficient experimental data to clearly establish a relationship for non-covalently bound Auger emitters. Preliminary indications based on data with ^{111}In-oxine (Refs. 63, 86, 104, and 105), ^{111}In-citrate (Refs. 63 and 86), ^{125}Iodoproflavine (Ref. 103) and trans-^{195m}Pt (Refs. 17 and 111) are that $H_{T,\text{AUGER}}$ will be about a factor of 2 less than that for the case of covalent binding to the DNA. Additional modifications to Eq. (8) may also be necessary if f_0 varies during the period the dose is delivered. We note that alternate approaches for prediction of dose-response for incorporated Auger electron emitters based on charged-particle fluence have been proposed by Younis and Watt.""""

E. Auger electron emitters for radiation therapy

The extreme biological effects associated with DNA-incorporated Auger emitters have led to their consideration for cancer therapy. Therefore, methods to predict the radiotoxicity of Auger emitters in therapeutic applications are necessary.[114] The formalism described above for calculation of equivalent doses may be useful in this regard. However, since sterilization of cells is of primary importance in radiation therapy (i.e., cell survival), a radiation weighting factor based on deterministic effects of Auger electrons $W_{R_{\text{Auger}}}$ should be employed. The extensive literature available on the deterministic effects of Auger emitters both *in vivo* and *in vitro* suggests that $W_{R_{\text{Auger}}}$ should be similar to that for high-LET alpha particles. Therefore, based on the relative biological effectiveness for deterministic effects of DNA-bound ^{125}I, this Task Group recommends that a preliminary value of 10 be used for $W_{R_{\text{Auger}}}$ in Eq. (8) to obtain the deterministic

equivalent dose H_T, for prediction of therapeutic outcome. As in the case of the equivalent dose for stochastic effects, when the Auger emitter is localized in the nucleus *but not covalently bound to DNA,* the value of $H_{T,R}$ Auger may be half the value for the DNA-bound case.

Evaluation of the potential of Auger pharmaceuticals for therapy not only requires the subcellular distribution of the radionuclide in the malignant cells, but also the degree of heterogeneity in cellular activity in the tumor.[82] This is of particular importance for Auger emitters labeled to thymidine precursors, since the uptake of these agents is cell cycle dependent. High uptake of a thymidine precursor in only a fraction of the tumor-cell population may result in selective sterilization of only a' subset of the tumor-cell population. Information on the heterogeneity of the cellular activity may only be obtained by autoradiographic techniques.[55,79,115] If the heterogeneity can be accurately quantified, it is possible in principle to calculate the absorbed dose on a cell-by-cell basis.[68,79,80,98,116,117] However, relating the absorbed doses calculated in this fashion to the overall biological effect remains a challenge.[118]

V. SUMMARY

Radionuclides that emit Auger electrons are widely used in biomedical research and nuclear medicine. When incorporated into the cell nucleus, these radionuclides are highly radiotoxic, causing biological effects akin to those caused by alpha particles. Whether for radiation protection or therapy, dosimetry of Auger emitters is important in order to predict their biological effects.[119,120] In this report we review the dosimetric techniques that have been employed in the context of observed biological effects, and we conclude that the techniques required depend on the biological system employed. Accordingly, methods of Auger electron dosimetry at the DNA, cellular, multicellular, and organ level are discussed. Subcellular distribution of the radionuclide plays a key role in all cases. The Task Group recommends the use of radiation weighting factors for cellular and organ dosimetry in conjunction with equivalent dose formalism that takes the subcellular distribution of the Auger emitter into account. Based on the currently available radiobiological data which show that the effects caused by Auger emitters are similar to those of incorporated alpha emitters, a preliminary radiation weighting factor of 10 is recommended for deterministic effects (i.e., cell survival) and a value of 20 for stochastic effects (i.e., risk assessment). The dose equivalent calculated with these weighting factors must be modulated by experimentally determined subcellular distributions. The preliminary formalism and radiation weighting factors suggested for equivalent dose calculations for Auger emitters can be updated as our understanding of the radiobiological effects of these radionuclides improves through experimental investigations using different Auger electron emitters and biological end points (e.g., transformation, mutation, etc.). In view of these recommendations for w_R Auger and the strong dependence of $H_{T,R}$ Auger on subcellular distribution, it may be prudent to review the current equivalent dose estimates for radiopharmaceuticals labeled with Auger electron emitters.

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