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DOSIMETRY OF AUGER EMITTERS: PHYSICAL AND PHENOMENOLOGICAL APPROACHES

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ABSTRACT

Recent radiobiological studies have demonstrated that Auger cascades can cause severe biological damage contrary to expectations based on conventional dosimetry. Several determinants govern these effects, including the nature of the Auger electron spectrum; localised energy deposition; cellular geometry; chemical form of the carrier; cellular localisation, concentration, and subcellular distribution of the radionuclide. Conventional dosimetry is inadequate in that these considerations are ignored. Our results provide the basis for biophysical approaches toward subcellular dosimetry of Auger emitters *in vitro* and *in vivo*.

INTRODUCTION

The MIRD Schema (Loevinger & Berman 1976) is widely used at present to estimate he biological risks of internal radionuclides. This conventional dosimetric approach assumes that radionuclides and the radiation energy are uniformly distributed in organs. Even though the cell is the basic unit at which biological effects are expressed, the calculated average dose to the organ is tacitly presumed to be the dose to the cell and its nucleus as well. The quality of radiation, the nature of the radiochemical, possible cellular concentration of radionuclides, and their subcellular distribution are ignored. In spite of this, conventional dosimetry has served as a reasonable approximation for energetic electrons, beta rays, and photons with ranges and mean free paths in biological matter greater than several cell diameters. In the case of Auger emitters, the above assumptions and inadequacies may severely restrict the

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validity of the conventional approach. It is true that Auger electrons carry only a small fraction of the energy released per decay, and contribute negligibly to the total organ dose. However, by spreading out their energy over macroscopic dimensions, conventional dosimetry trivializes the likely importance of these low energy Auger electrons.

The biological implications of Auger emitters have been of interest for nearly 20 years. The severe toxicity of DNA incorporated ^{125}I has been demonstrated repeatedly in various cell systems. Our *in vitro* and *in vivo* studies (Kassis et al. 1987, Rao et al. 1987) show that Auger emitters cause biological damage depending on their localisation relative to the cell, its nucleus, and the DNA which is the primary target of radiation action. The biological dosimetry and biophysical results emerging from these studies provide an experimental data base for meaningful approaches to the dosimetry of Auger emitters at the subcellular level. We examine some of the physical and phenomenological aspects in this paper.

PHYSICAL CONSIDERATIONS

Auger cascades

Photoelectric effect and nuclear decay by orbital electron capture (EC) and internal conversion (IC) cause inner shell ionisation of atoms. The complex atomic vacancy cascades that follow are dominated by nonradiative (NR) Auger, Coster-Kronig (CK) and super CK processes illustrated in Figure 1 (Sastry & Rao 1984). In each NR transition filling a vacancy, two new vacancies are created in the higher atomic subshells. This vacancy multiplication, and the progressively decreasing transition energies result in a dense shower of low energy electrons (~20 to 500 eV) with very short ranges (~1 to 20 nm) in biological matter. The review by Sastry & Rao (1984) of the physics and biophysical dosimetry of Auger cascades contains tables of average Auger and CK electron spectra calculated for several radionuclides of interest. Relevant references may be found therein. Figure 2 indicates the complexity of the electron spectrum. The results shown for ^{111}In decay are obtained using Monte Carlo methods (Charlton & Booz 1981, Howell et al. 1986) assuming no appreciable charge buildup on the ^{111}Cd daughter in the condensed phase. The electron groups at the extreme right (Fig. 2) are due to IC. Table 1 is a summary of average Auger and CK electron yields for several radionuclides. Electrons with very low energies (< 500 eV) are preponderant in each case. The

Figure 1. Nonradiative atomic vacancy transitions.

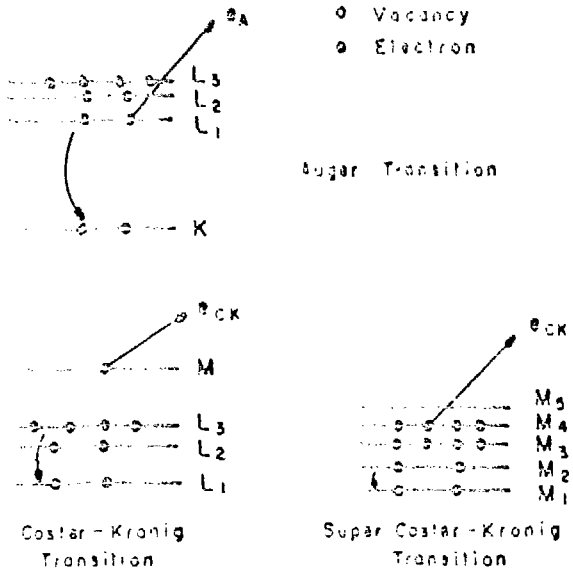
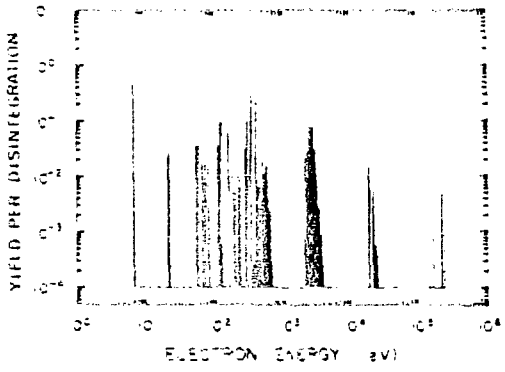


Figure 2. Electron spectrum for ^{111}In decay.



Auger yields depend on the atomic number, EC and IC probabilities, and the number of steps in isomeric decays (e.g., ^{193m}Pt & ^{195m}Pt). In a single decay, the electron spectrum depends on the relaxation pathways, and it can be very different from the average spectrum.

Localised energy deposition: High LET effects

Densely ionising α-particles, with their high linear energy transfer (LET) of about 100 keV/μm in unit density matter, are very efficient in inducing biological effects. The low energy Auger electrons have LET values ~15 to 25 keV/μm (Cole 1969). Simultaneous ejection of several cascade electrons should be expected to simulate high LET-type effects in the immediate vicinity of the decay site. Using the methods of Kassis et al. (1980), we have calculated the average energy (ΔE) deposited by the electrons in a unit density sphere, 5 nm in radius, around the decay site. These results, obtained in the continuously slowing down approximation (csda), are given in Table 1. Possible contributions from potential energy on the ion are not included. Figure 3 shows the energy absorbed in concentric spherical shells of various radii, centered on the Auger emitter (^{193m}Pt, ^{111}In & ^{55}Fe). These curves (Wright et al. 1987) are the results of Monte Carlo calculations for liquid water using the Oak Ridge Electron Transport Code. The dashed curve for ^{193m}Pt, obtained using the average spectrum and csda, compares reasonably with the Monte Carlo results. This illustrates the utility of simple and approximate methods, especially in view of basic uncertainties in atomic transition rates and energies in the near-valence region. The differential profile of energy density around the Auger emitters ^{125}I and ^{193m}Pt is shown (Fig. 4) by the dashed and solid curves, respectively. These results indicate the pattern of the highly localised energy deposition (HILED), the energy density dropping precipitously by two orders of magnitude in the first 5 nm. Considering that 10 eV/(nm)^3 implies a local dose equivalent of 1.6 MGy in commonly understood terms, the data bring to light the implications of small energy depositions in extremely minute volumes. Figure 5 shows that the high density of chemical species (dots) around the Auger emitter ^{193m}Pt in liquid water is comparable with the density of species along the track of a 4-MeV alpha particle (Wright et al. 1987).

Figure 3. Localised energy deposition.

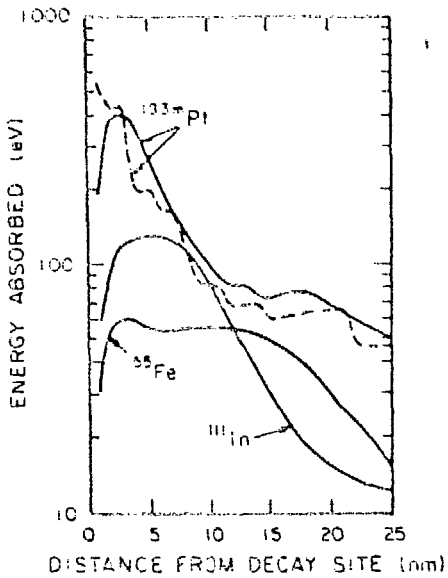


Table 1. Average yields of Auger and CK electrons and localised energy deposition for some radionuclides.

Radionuclide	Average yield per decay*	Energy (eV) deposited in a 5 nm sphere
^{51}Cr	6 (5)	210
^{55}Fe	5 (3)	240
^{67}Ga	5 (3)	260
^{75}Se	7 (5)	270
^{77}Br	7 (5)	300
^{99m}Tc	4 (4)	280
^{111}In	8 (7)	450
^{125}I	19 (17)	1000
^{193m}Pt	27 (23)	1800
^{195m}Pt	33 (27)	2000
^{201}Tl	20 (17)	1400

*Low energy electron yield is given in parentheses.

Figure 4. Profile of absorbed energy density.

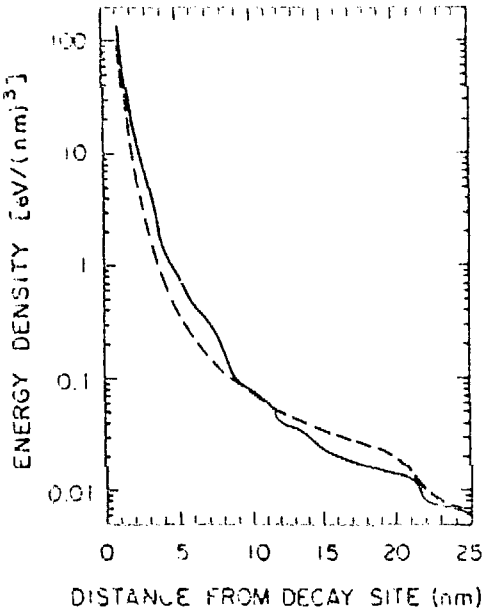
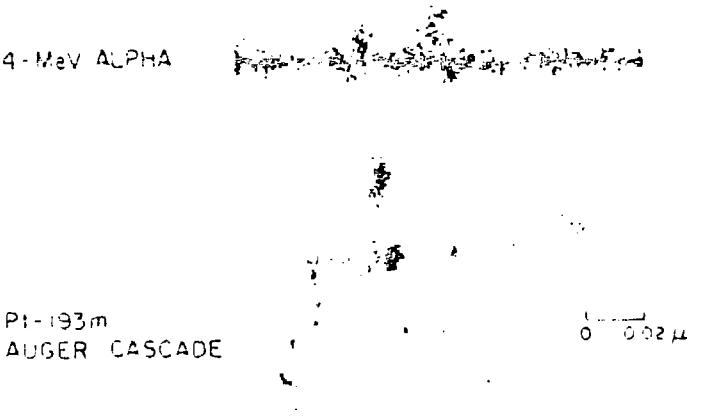


Figure 5. Track structure in liquid water for a 4-MeV alpha particle and ^{193m}Pt Auger cascades.



BIOPHYSICAL ASPECTS

Positional and concentration effects

Values of ΔE in Table 1, the patterns of HILED (Fig. 3 & 4), and the high density of chemical species in the immediate vicinity of the decay site of the Auger emitter (Fig. 5) indicate the potential for severe damage of molecules in the neighbourhood. The *in vitro* studies (Kassis et al. 1987) show that ^{125}I and ^{77}Br, covalently bound to the DNA of Chinese hamster V79 cells, kill the cells efficiently, the relative biological effectiveness (RBE) being 6-7. The RBE of ^{125}I attached to a DNA intercalator is about 5 for the same cell line. The drug *trans*-platin (II) forms adducts with the DNA. Our recent work shows that, when cells are exposed to this platinum-coordinated complex labeled with ^{195m}Pt, the RBE of this Auger emitter is also about 5. In contrast, ^{125}I in the nucleus but not bound to DNA is not so efficient (RBE ~1.7). Decays of ^{125}I and ^{75}Se in the cytoplasm are mildly radiotoxic, while extracellular decays of ^{125}I and ^{77}Br are much less so. The radiotoxicity of ^{51}Cr stems from the fact that 15% of the activity in the cell is in its nucleus. The *in vivo* effects also depend on the localisation of the Auger emitter (Rao et al. 1987). When ^{75}Se remains in the cytoplasm of testicular cells and in the intertubular spaces, the RBE is essentially unity. For ^{111}In-oxine, with 92% of the cellular radioactivity in the nucleus, the RBE is about 4. The RBE is much lower for ^{111}In-citrate with only 30% of intracellular ^{111}In present in the nucleus. The effects of low energy electrons should depend on the location of the Auger emitter. These studies confirm such a dependence and quantify the effects as a function of the location of the radionuclide.

The experimental studies clearly reveal the importance of the chemical nature of the carrier in determining the subcellular distribution of the radionuclide. Cells *in vitro* concentrate some radionuclides greatly (Kassis et al. 1985, 1987). Relative to extracellular concentration, $^{125}IUdR$ concentration in the nuclei of V79 cells is 1850-fold larger, after an 18-hr incubation at 37°C. For ^{75}Se-methionine, the cellular concentration factor n = 330, and for $^{201}TlCl$, n = 130. The ^{201}Tl studies, in fact, demonstrate that cellular localisation of this Auger emitter is essential for manifestation of its biological effects (Kassis et al. 1983). The *in vivo* studies cannot easily establish evidence for concentration of radionuclides by testicular cells. Nevertheless,

biochemical mechanisms *in vivo* and *in vitro* should be reasonably similar, and cellular concentration of radionuclides should be one of the determinants of the effects of Auger emitters.

Subcellular energy deposition

The above considerations point to the importance of the energy deposited in the target cell and its nucleus from decays occurring within the cell. Kassis et al. (1980) have calculated the energy deposited in the cytoplasm and in the nucleus of V79 cells from decays in the respective compartments assuming that the nucleus and the cell are concentric spheres of unit density (Fig. 6). Hypothetical radionuclides, emitting monoenergetic electrons with unit yield, are assumed to be distributed uniformly in the cytoplasm (Cy) or the nucleus (N) of the cell. Values of energy deposited - ϵ_{NN}, ϵ_{NCy} and ϵ_{CyCy} - are calculated as a function of the electron energy per decay. The first subscript represents the target region, and the second one, the source region. The results do not depend strongly on deviation from spherical geometry but do depend on the nuclear radius R_N and the cell radius R_C. Figure 7 shows the results for cells with R_C = 4.5 μm and R_N = 2.5 μm, the average geometry of spermatogonial cells in our mice.

REALISTIC DOSIMETRY

Cells in culture

In these studies, suspended cells are kept separated by shaking during incubation. The dose to the target cell nucleus is the sum of the dose from decays external to the cell (E_{Ne}) and from internal decays (E_{NN} and E_{NCy}). The total amount of energy deposited in the nucleus $E_N = E_{NN} + E_{NCy} + E_{Ne} = d_t \epsilon_N$. The contribution of E_{Ne}, calculated using MIRD Schema, is negligible. The quantity $\epsilon_N = r_N \epsilon_{NN} + r_{Cy} \epsilon_{NCy}$, where r_N and r_{Cy} are, respectively, the nuclear and cytoplasmic fractions of intracellular radioactivity. The cumulated number of decays in the cell, d_t, is the sum of the disintegrations occurring during incubation (d_I), and postincubation (d_{PI}). These are experimentally determined from uptake data during incubation, and from postincubation retention studies, both as a function of time. Values of ϵ_{NN} and ϵ_{NCy} are obtained for each radionuclide using its electron spectrum and the generalised energy deposition curves similar to those in Figure 7. For ^{125}I, ϵ_{NN} = 11.2 keV/decay and ϵ_{NCy}= 0.86 keV/decay. The vast

Figure 6. Geometry for calculation of subcellular energy deposition. See Kassis et al. (1980) for details.

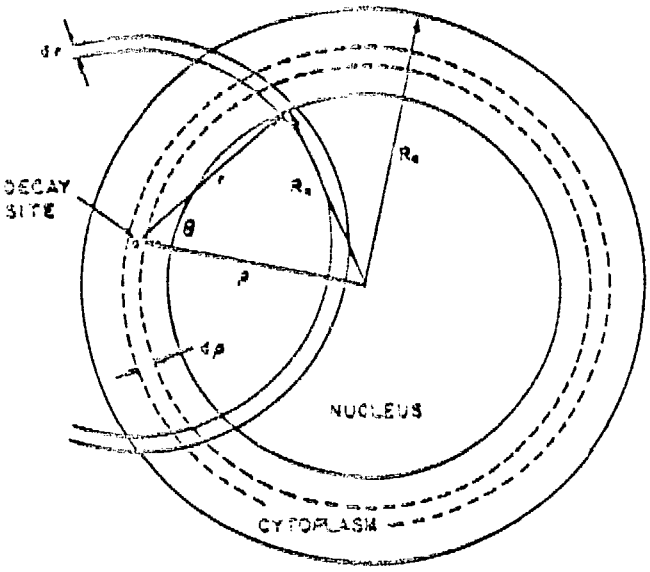
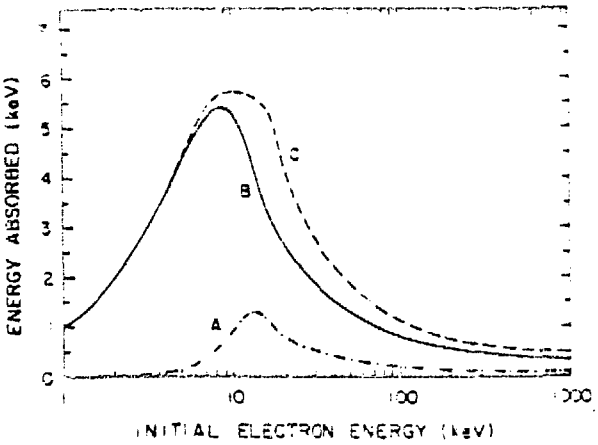


Figure 7. Generalised energy deposition curves for spermatogonial cells: Curves A, B and C represent ϵ_{NCy}, ϵ_{CyCy} and ϵ_{NN}, respectively. See text.



difference between the two shows the high efficacy of decays in the nucleus compared to those in the cytoplasm.

Spermatogonial cells: Dose enhancement

The actual dose received by the nuclei of cells should be larger than conventional estimates in view of possible concentration of the Auger emitter by cells. For cells in culture, all the variables are generally known and the cumulated dose is readily calculated. This is not so for spermatogonial cells *in vivo*. We have, therefore, introduced a dose enhancement factor (N_N) (Rao et al. 1985). Here $N_N = R_N/R_{CON}$, R_N being the actual instantaneous rate of energy deposition in the target nucleus from decays within the cell and from the external region, and R_{CON}, the conventionally calculated value. The following expression for N_N is readily derived:

$$N_N = \{(n/f_N)(r_N\Phi_{NN} + r_{Cy}\Phi_{NCy})/[f_c(n-1) + 1] + \Phi_{Ne} + \Delta\}(1 + \Delta)^{-1}, \quad (1)$$

where f_c = fraction of the testicular volume occupied by the spermatogonial cells, and f_N = fraction of the spermatogonial cell volume occupied by its nucleus. The quantities Φ_{NN} and Φ_{NCy} are, respectively, the ratios of electron energy absorbed in the target nucleus to the electron energy emitted per decay in the nucleus, and in the cytoplasm of the target cell. The parameter Φ_{Ne} is the ratio of electron energy absorbed in the target nucleus to the electron energy emitted per decay external to the target cell. The symbol Δ is the ratio of photon energy absorbed in the testis to the electron energy emitted per decay in the organ. The variables n, r_N and r_{Cy} are defined earlier.

In equation (1), Φ_{Ne} and Δ are essentially given by conventional dosimetry. For the measured cellular geometry, $f_N = 0.171$. The absorbed fractions Φ_{NN} and Φ_{NCy} are determined using the results in Figure 7 and the electron spectra for various Auger emitters. The subcellular distributions (r_N and r_{Cy}) are measured. Thus, n and f_c are the free variables. For spermatogonia in the 10 μm basal layer of the tubules (diameter 100 μm), a value of $f_c \approx 0.1$ is a reasonable one (Rao et al. 1983). Values of N_N are predicted consistent with the observed RBE values (Rao et al. 1987) for reasonable values of n. Examples of the parameters are given in Table 2. The respective experimental RBE

Table 2. Parameters in the dose enhancement factor.

Parameter	^{55}Fe-citrate	^{111}In-oxine	^{111}In-citrate
r_N	0.15	0.92	0.30
r_{Cy}	0.85	0.08	0.70
ϕ_{NN}	0.89	0.122	0.122
ϕ_{NCy}	0.016	0.0048	0.0048
ϕ_{Ne}	0.0	0.892	0.892
Δ	0.332	0.114	0.114

values for ^{55}Fe-citrate, ^{111}In-oxine and ^{111}In-citrate are 2.6, 4.3 and 2.0. Equation (1) predicts these values for N_N with n = 5 (^{55}Fe), n = 12 (^{111}In-oxine), and n = 10 (^{111}In-citrate).

CONCLUSION

In this paper, we have examined the nature of HILED primarily responsible for the high LET-type effects of Auger emitters close to or incorporated into DNA. The possible role of potential energy on the ion needs further investigation. The prevalence of highly localised doses around the site of the emitter should be expected to cause a variety of severe lesions in the DNA. This feature may have implications for radiotherapy and public health. We have found that calculation of doses to the nucleus is reasonable even when Auger emitters are DNA-bound. The dose enhancement factors (N_N) are based on our phenomenological results, and the parameters are identified. The expression for N_N adequately explains the observed RBE values in the mouse testis. The results of primary oocyte studies are, in principle, understandable along similar lines. Our model for N_N is also relevant to the <u>in vitro</u> situation where $f_c \approx 0$. At 37% survival, we estimate a value of about 1,000 for N_N in the case of V79 cells incubated with ^{125}IUdR for 18 hr. This illustrates the inadequacy of conventional dosimetry for situations <u>in vitro</u>. When f_c has values of about 0.7 for highly packed cell systems, $N_N \rightarrow 1$ even for large values of n. In this limit, as well as when $n \rightarrow 0$, conventional dosimetry is essentially valid.

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REFERENCES

Charlton, D.E. & Booz, J., 1981, Radiation Research, 87, 10.

Cole, A., 1969, Radiation Research, 38, 7.

Howell, R.W., Sastry, K.S.R., Hill, H.Z. & Rao, D.V., 1986, Cis-Platinum-193m: Its microdosimetry and potential for chemo-Auger combination therapy of cancer. In Proceedings of 4th International Radiopharmaceutical Dosimetry Symposium, CONF 85-1113, edited by A.T. Schlafke-Stelson & E.E. Watson, p. 493.

Kassis, A.I., Adelstein, S.J., Haydock, C. & Sastry, K.S.R., 1980, Radiation Research, 84, 407.

Kassis, A.I., Adelstein, S.J., Haydock, C. & Sastry, K.S.R., 1983, Journal of Nuclear Medicine, 24, 1164.

Kassis, A.I., Sastry, K.S.R. & Adelstein, S.J., 1985, Radiation Protection Dosimetry, 13, 233.

Kassis, A.I., Adelstein, S.J., Howell, R.W. & Sastry, K.S.R., 1987, Positional effects of Auger decays on mammalian cells in culture. In Proceedings of International Workshop on Auger Emitters in DNA: Implications and Applications, edited by K.F. Baverstock & D.E. Charlton (Taylor & Francis) p.

Loevinger, R. & Berman, M., 1976, Medical Internal Radiation Dose Committee Pamphlet No. 1, Revised (Society of Nuclear Medicine).

Rao, D.V., Sastry, K.S.R., Govelitz, G.F., Grimmond, H.E. & Hill, H.Z., 1985, Journal of Nuclear Medicine, 26, 1456.

Rao, D.V., Mylavarapu, V.B., Sastry, K.S.R. & Howell, R.W., 1987, Internal Auger emitters: Effects on spermatogenesis and oogenesis in mice. In Proceedings of International Workshop on Auger Emitters in DNA: Implications and Applications, edited by K.F. Baverstock & D.E. Charlton (Taylor & Francis) p.

Sastry, K.S.R. & Rao, D.V., 1984, Dosimetry of low energy electrons. In Physics of Nuclear Medicine: Recent Advances, edited by D.V. Rao, R. Chandra & M. Graham (Medical Physics Monograph No. 10)(American Institute of Physics), p. 169.

Wright, H.A., Hamm, R.N., Turner, J.E., Howell, R.W., Sastry, K.S.R., Rao, D.V. & Haydock, C., 1987, Abstracts: Thirty-fifth Annual Meeting of the Radiation Research Society, Abstract Cr-3, p. 48.

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