Biophysical Aspects of Auger Processes, AAPM Symposium Series No. 8 (1992) 001-013
Eds. RW Howell, VR Narra, KSR Sastry, DV Rao

BIOPHYSICAL ASPECTS OF AUGER PROCESSES: A REVIEW OF THE LITERATURE 1987-1991

S. JAMES ADELSTEIN

Department of Radiology
Harvard Medical School
Boston, MA 02115, USA

ABSTRACT

The workshop on Auger emitters held in Oxfordshire in 1987 produced papers on physical dosimetry, molecular damage, biologic effects, and therapeutic applications. These are briefly summarized. Since that time there has appeared in the literature a number of reports on Auger processes as they relate to microscopic and cellular dosimetry, DNA damage, biologic consequences, and therapeutic potential. A number of these are reviewed as background for the Second International Symposium.

THE WORKSHOP OF 1987

On opening this Second International Symposium, I thought it profitable to begin where we left off at Charney Bassett four years ago. As I had the honor of closing that first meeting, I was able to refer to my own notes as well as to the excellent volume of proceedings prepared by Keith Baverstock and David Charlton (1). The principal themes of that symposium can be divided into physical dosimetry, molecular damage, biologic effects, and therapeutic applications.

Physical Dosimetry

It had been realized for some time that conventional dosimetry significantly underestimates the energy deposited in radiosensitive targets when Auger emitters are affixed to DNA. Sastry showed that a better approximation is made by calculating the dose to the nucleus rather than averaging over all cells, cell compartments, and extracellular regions as in the MIRD and ICRU methodologies. Charlton presented a Monte Carlo approach to following each electron track so that a precise statistical estimate can be made of energy deposited per base in the DNA immediately surrounding the decay, and, by inference, of the number of single strand breaks (SSB) and double strand breaks (DSB) created. Humm extended this model to photoelectric interactions with inner shell electrons of incorporated nonradioactive bromine, concluding that the consequent Auger shower would only provide a small increment of damage above the usual sensitization. This last point, one of some contention, was on the verge of being settled by data from a new synchrotron source being applied to this problem in Japan by Ito, Ohara and Maezawa.

Molecular Damage

Molecular biologic approaches were employed by Martin who used a Hoechst dye (33258) labeled with ^{125}I that binds to certain A-T-rich regions of DNA. The labeled compound produces clusters of SSB and DSB at the binding site, while the unlabeled parent compound protects against DNAase degradation in the same regions, demonstrating again the "microsurgical" quality of DNA shattering produced by Auger emitters when brought into close proximity to the DNA. On the other hand, Baverstock presented an argument that certain experimental results in which ionizing energy is directly deposited in phage and plasmid DNA can be explained by long-range

(μm) transfer of excitation energy in DNA. He postulated a mechanism involving solitons and proposed that the hypothesis could be tested using the energy released on decay of ^{125}I incorporated at a specific site in a DNA molecule.

Biologic Effects

A number of biologic consequences were also elucidated. High-LET-like survival curves were seen not only with Auger emitters incorporated into DNA but also with ^{125}I brought into contact with DNA by way of thyroid hormone receptors as reported by Sundell-Bergman, by intercalators as discussed by Kassis and by dye-binding (*vide supra*). The importance of DSB as lethal lesions was stressed by Radford who pointed out that 60 DSB are found per lethal event with ^{125}I, while 83 DSB are found per lethal event with X rays. In his experiments, survival, chromosomal aberrations, and DSB were coincident. In addition, the site of labeling within the genome seemed of critical importance as determined from differential 5-[^{125}I]iodo-2'-deoxyuridine ($^{125}IUdR$) labeling within S phase by Kassis and aphidicolin-directed labeling by Yasui. The possibility that the function of the DNA that is damaged by an Auger cascade may be important in terms of the outcome at the cellular level was suggested by Apelgot. Other biologic end points being examined included mutagenesis by Fujiwara and gene amplification by Lucke-Huhle.

Therapeutic Applications

Lastly, a number of practical therapeutic applications were being tested. Bagshawe reported on the pharmacologic manipulation of $^{125}IUdR$ incorporation into the DNA of human tumors, and Brown on the use of tumor-targeting iodinated naphthoquinols, which also localize in the cell nucleus.

PUBLISHED REPORTS 1987-1991

I have taken as my further assignment a review of the literature published in the interval. There is no pretension that this review is complete or that the categories I have chosen would correspond with those of others.

Microscopic and Cellular Dosimetry

A number of papers on various aspects of dosimetry have appeared. Younis and Watt (2) have calculated the cross section for inactivation of ^{125}I, ^{77}Br, ^{3}H and ^{131}I from the slowing down charged particle fluence and published survival data. They conclude that ^{125}I, ^{77}Br, and ^{3}H have qualities approaching those of heavy particles. They infer from their results that the damage from ^{125}I and ^{77}Br is mostly direct and that from ^{3}H mostly indirect. All results are consistent with the interpretation that electron damage is caused predominantly at the end of the tracks. The Younis and Watt hypothesis stands in contrast to that of Goodhead (3) who has suggested "at all subcellular levels, even down to DNA, high linear-energy-transfer (LET) radiations can produce unique initial damage, different from that possible with low-LET radiations, and therefore may even, in principle, produce unique final biological effects."

Booz *et al.* (4) have tried to distinguish between ^{125}I specifically incorporated into DNA and the radionuclide homogeneously deposited in tissue. They have also tried to determine the importance of the charge transfer phenomenon. With reference to insights obtained from local dose profiles using electron ranges and stopping power, the Monte Carlo calculation of Auger-electron cascades, number distributions and energy spectra, the application of track-structure calculations to the disintegration of ^{125}I as well as the precise evaluation of local energy density produced by multiple charge on the atom after decay, they calculate total potential energy on "isolated" daughter atoms of ^{125}I after termination of the Auger-electron cascade. Since the energy potential due to multiple ionization is about equal to that due to the deposition of Auger electrons, they feel it is useless to separate these two effects by radiobiologic methods. They also estimate that for ^{125}I incorporated into specific biologic targets of 20 nm, most of the energy deposited is above 40 keV/μm and does not need to be subclassified. For the nonspecific, homogeneous incorporation of ^{125}I, about 20% of the energy deposited in 25 nm critical targets is made up from decays from those targets, while the remaining 80% of the dose is from low-LET radiation outside of the targets. Halpern (5) disagrees with their first conclusion. Evidence that the chemical nature of the component molecule or the solvent plays a role in the dissipation of charge (primarily through the presence or absence of π electron resonances) leads him to believe that the stacking of bases in DNA can be responsible for long-range effects due to this mechanism.

At the cellular level, there seems little doubt that the intranuclear localization of Auger-electron emitters is required to observe the biologic effect of the Auger process. Kassis *et al.* (6) have reported that with V79 cells mitochondrial-bound (cytoplasmic) ^{125}I produces a cytocidal survival curve having a distinct shoulder and a mean lethal dose (D_{37}) of 462 cGy, while ^{125}I incorporated into DNA produces a logarithmic survival curve with a D_{37} of 80 cGy. Link *et al.* (7) working with radiolabeled methylene blue, a dye that binds to the cytoplasmic melanin granules of melanoma cells, have shown that conspicuous cytocidal effects are obtained when the agent is labeled with the α particle emitter ^{211}At but not with the Auger-electron emitter ^{125}I.

A number of investigators have obtained similar results with ^{111}In. Rao *et al.* (8) have compared the ability of ^{111}In oxine, ^{111}In citrate, ^{114m}In citrate and X rays to reduce the spermhead population in mouse testes. The D_{37} of the four agents is 16 cGy, 34 cGy, 57 cGy and 67 cGy, respectively. The difference between ^{111}In oxine and ^{111}In citrate is ascribed to the higher nuclear fraction of the former (92% versus 30%). In the case of ^{114m}In, only 0.8% of the dose comes from Auger electrons, whereas in the case of ^{111}In, 20% comes from Auger electrons.

McLean and Wilkinson (9) have studied the survival of V79 cells *in vitro* after exposure to ^{111}In. They reckon that the dose to the cells from intranuclear decay is 3.5 mGy and from extracellular decay, 5.8 pGy, a considerable difference. McLean *et al.* (10) have demonstrated that ^{111}In oxine, some of which is tightly bound to chromosomal DNA, is a potent producer of chromosomal aberrations, while extracellular ^{111}In chloride is a much weaker one.

A number of investigators have been concerned that traditional dosimetry schemes (such as MIRD) underestimate the doses to specific population groups within tissues when Auger-electron emitting radionuclides are concentrated by cells and especially by the cell nucleus. Bialobrzeski *et al.* (11) have shown for ^{51}Cr-bleomycin that the doses calculated for cell nuclei and DNA in liver cells are higher than the cell-averaged values by factors of 2.5 and 5, respectively, and the corresponding dose equivalents (taking into account the quality factor for Auger showers) by factors of 9 and 24. Similar thinking has been applied to ^{51}Cr labeled lymphocytes by Vezza *et al.* (12), who calculate the actual dose to be twice the conventionally calculated one.

Makrigiorgos *et al.* (13) have also written about the limitations of conventional internal dosimetry at the cellular level. They have prepared a model that takes into account the intracellular-to-extracellular radionuclide concentration and the labeled cell density for radionuclides ^{99m}Tc, ^{201}Tl, ^{111}In and ^{123}I, all commonly used in the practice of nuclear medicine. They have shown that when selective intracellular uptake of a radiolabeled compound occurs in specific cells within a cell cluster, conventional dosimetry underestimates the radiation dose delivered to the labeled cells by two fold to more than 25-fold if the emitted electrons have ranges of a few micrometers or less. Under the same conditions, conventional dosimetry overestimates slightly the electron dose to the nonlabeled cells. This approach has been applied to the irradiation of liver and spleen macrophages by ^{99m}Tc labeled microaggregates (14) and of lung capillaries by ^{99m}Tc labeled macroaggregates (15). In the case of the lung, ascribed doses to some individual cells were found to be as high as 30,000 times the calculated average dose.

DNA Damage

The damage to DNA from Auger processes continues to fascinate a number of investigators, as indeed it should. Charlton and Humm (16) have refined the model presented at the Oxford meeting, which can be used to calculate initial DNA strand breakage following the decay of ^{125}I. DNA is again modeled as a 2.3 nm cylinder with a 1 nm base-pair core and the Paretzke electron track code is employed to calculate the energy deposited in the sugar-phosphate and base volumes. Two spectral sources are used, the original of Charlton and Booz and a newer one of Pomplun (*vide supra*), in which the charge energy is handled differently. Two types of SSB and three of DSB are recognized. The distribution of SSB fits the experimental results of Martin and Haseltine, while values between 0.82 to 1.07 DSB per decay are obtained depending on the electron spectra postulated.

Using their own method of calculating spatial energy distribution from low-energy electrons and the ^{125}I Auger-electron spectrum of Charlton and Humm (16), Unak and Unak (17) calculate that about one keV of energy is absorbed in regions of DNA 2 nm from the decay site in both directions. When they assume that 5 eV deposited in DNA produces a SSB, they reckon that local absorption of ^{125}I Auger electrons is able to produce at least one DSB without taking into account neutralization effects from the highly charged residual tellurium ion.

Some investigations have begun into the relative role of direct and indirect damage in DNA from Auger cascades. Wright *et al.* (18) have made Monte Carlo calculations for the physical and chemical interactions of Auger electrons with liquid water. They have illustrated the distribution of watery radicals in the vicinity of a DNA duplex and calculated the yields of each aqueous species from the decay of a number of radionuclides. For ^{125}I decaying on the surface of a DNA cylinder, they calculate 44 indirect and 21 direct interactions per disintegration, or an indirect/direct ratio of about 2/1.

Recently, Pomplun (19) has produced a new DNA target model for track structure calculations and applied it to the interaction of ^{125}I Auger electrons. He elaborates electron track interactions in a cylindrical model of DNA 14.3 nm long and 2.4 nm in diameter. (In contrast to the Wright model (18), he has the decay taking place within the cylinder.) In a series of histograms, he shows mean energy deposited by direct and indirect hits in phosphate-sugar strands and bases both on the ipsilateral and contralateral labeled filaments. As expected, the fraction of direct hits is greater on the contralateral strand. Assuming a minimum of 10 eV direct energy and 17 eV indirect energy to produce a strand break, Pomplun calculates 1.8 of a total 3.8 SSB per decay are caused by direct interactions. Of the 0.94 DSB produced per decay, about 40% are due to direct action.

Makrigiorgos *et al.* (20) have compared DNA damage produced in V79 cells by incorporated ^{123}I with that of ^{125}I. Using neutral elution, they have measured DSB production in frozen cells. They have also compared their experimental results with theoretical ones derived from the Charlton and Humm model (16). They have found ^{125}I to be 1.3 times as effective as ^{123}I in producing DSB, whereas theory has predicted it would be 1.6. If one assumes that each decay of ^{125}I produces one DSB, then each decay of ^{123}I produces, on average, 0.74 DSB.

Martin *et al.* (21) have measured the induction of double strand breaks in plasmid DNA following neutron capture by ^{157}Gd. The (n,γ) reaction results in ^{157}Gd and is accompanied by internal conversion. The DSB are thought to be generated by the resulting Auger cascade, as they are produced only when the ^{157}Gd is bound to DNA and not when the atom is sequestered by EDTA.

Biologic Consequences

At the biologic level, a number of observations have been made, the first group involving photon activation. Nath *et al.* (22) have studied survival of Chinese hamster cells exposed to low-energy photons after IUdR incorporation. The enhancement of IUdR sensitization is about 1.5 for 250 kVp X rays relative to 4 MV X rays and 1.4 and 2.7 for the 60 keV photons of ^{241}Am compared to the 860 keV photons of ^{226}Ra when IUdR replacement of thymidine is 5 and 25%, respectively. The authors ascribe the enhanced sensitization to the Auger effect. In comparison, Miller *et al.* (23) have examined the radiosensitization of V79 cells in which 16% of the thymidine residues have been replaced with IUdR. Enhancement ratios at the 1% survival level are 1.8 for 15 MV and 1.95 for 100 kVp radiation. This modest 10 to 15% additional enhancement with 100 kVp X rays is much less than that predicted by the proponents of photon activation therapy.

Larson and colleagues (24) have examined the Auger electron contribution to bromodeoxyuridine radiosensitization in V79 cells. When cells with 32% of thymidine residues replaced by BrUdR are exposed to monoenergetic X rays just below (13.450 keV) or above (13.490 keV) the K edge (13.475 keV) of bromine, enhancement ratios of 3 to 12% are obtained depending on the means of calculation; most values are between 5 and 7%. The authors conclude that Auger electrons produced following photoelectric absorption of X rays by the K shell of bromine contribute minimally to observed BrUdR cellular radiosensitization. In a simpler system, the radiolysis of bromodeoxyuridine-monophosphate, Takakura (25) has compared the effects of 13.49 and 13.43 keV X rays. The ratio of G values for the formation of the major product, dUMP (debrominated Br-dUMP), is 2.2, and for the conversion of dUMP to uracil, 1.0. The author believes the results confirm that Auger electrons stripped from the K shell of bromine play the major role in the radiolysis of the nucleotide.

Another set of experiments is concerned with the relative biologic effectiveness (RBE) of Auger emitters with themselves and other forms of radiation. Kassis *et al.* (26) have looked at the relative effectiveness of ^{125}I, ^{123}I and ^{77}Br on the survival of V79 cells. They find that the mean lethal dose (D_{37} survival) to the nucleus is about 80 cGy in all cases. However, the total number of decays needed to produce this D_{37} is about twice as much with ^{123}I as with ^{125}I, approximately equal to the ratio of the energy deposited in

microscopic volumes by ^{125}I and ^{123}I, respectively. When applied to 5 nm diameter spheres, all three radionuclides lie on the same line in an inverse plot of deposited energy versus decays required for 37% survival.

Pomplun *et al.* (27) have calculated the equivalence of ^{125}I decays to high-LET radiation. In sensitive biologic volumes of 20 nm, they reckon a mean lineal energy equivalent of 270 keV/μm. They have tabulated published RBE values for a number of biologic end points. For chromosomal aberrations, the values scatter between 6 and 77, for transformations between 32 and 38, and for mutations between 1 and 16. These values can be compared to the recommended ICRP quality factor of 20 for this level of LET, *i.e.*, 270 keV/μm.

Rao *et al.* (28) have examined the effects of radiations of different quality on spermhead survival and the induction of spermhead abnormalities. They find an RBE of 6.7 for ^{210}Po α particles and 7.9 for DNA-bound ^{125}I when compared with 60 or 120 kVp X rays for spermhead survival. For abnormalities, the corresponding values are 245 and 59. Using ^{7}Be, a monoenergetic photon emitter (477 keV), a dose rate effect is demonstrated which should be taken into account when comparing acute and chronic exposures.

Whaley and Little (29) have addressed the issue of mutation induction by incorporated radioiodine. They have examined the mutational frequencies at the hprt locus for cells proficient (TK6) and deficient (SE30) in thymidine kinase, an enzyme necessary for the incorporation of IUdR into DNA. For cells proficient in thymidine kinase, the D_0 values for $^{125}IUdR$, $^{131}IUdR$ and X rays are 5.9, 24 and 75 cGy, respectively. No cell death can be produced in the deficient cells with $^{125}IUdR$; for $^{131}IUdR$ and X rays the corresponding D_0 values are 54 and 77 cGy. The induced mutant fraction for $^{125}IUdR$ in the proficient cells is 3.3×10^{-6} per cGy, for $^{131}IUdR$, 0.45×10^{-6}, and for X rays, 0.05×10^{-6}. In deficient cells, no mutants are induced by $^{125}IUdR$; for both $^{131}IUdR$ and X rays the induced fraction is 0.04 to 0.05×10^{-6}. The results demonstrate clearly the extraordinary ability of incorporated ^{125}I to produce mutations as well as cytocidal effects. The RBE of ^{125}I relative to ^{131}I for survival is 4.0; for mutations, 7.3; the RBE of ^{125}I relative to X rays is 12.7 for survival and 66 for mutations. Whaley *et al.* (30) have also shown that the DNA intercalating agent ^{125}I-iodoacetylproflavine (^{125}IAP) can induce mutations at both the hprt and tk loci. When these results are compared with those observed with $^{125}IUdR$, ^{125}IAP shows a reduced effectiveness per decay; for survival the RBE is between 2 and 4, for mutations at the hprt locus

between 3.5 and 6. ^{125}IAP treatment induces large-scale genetic events at the hprt locus at high frequency in comparison to X rays, 90 versus 50%.

Therapeutic Potential

A keen interest in the potential use of Auger-electron emitters for targeted radionuclide therapy continues. Humm and Charlton (31) have developed a method to assess the therapeutic potential of Auger-electron emission. Their projection depends on electron track structure methods and the prediction of double strand breaks presented earlier (*vide supra*). According to their calculations, the DSB produced per decay of ^{125}I, ^{123}I and ^{77}Br incorporated into DNA are 1.10, 0.73 and 0.38, respectively. An advantage of ^{125}I with its 60 d half-life is that relatively few atoms need be incorporated into the genome for effective tumor sterilization. Humm *et al.* (32) have also focused on ^{123}I and ^{77}Br as alternatives to ^{125}I therapy based on results with experimental tumors using ^{125}IUdR. Baranowska-Kortylewicz *et al.* (33) have demonstrated that ^{123}IUdR can be used effectively for the diagnosis and therapy of ovarian ascites tumors in mice. The diagnostic capability stems from the 140 keV photon emitted by ^{123}I, which is suitable for imaging.

Anderson and Holt (34) and DeSombre *et al.* (35) have examined the potential of estrogens labeled with ^{125}I, ^{123}I and ^{80m}Br for the therapy of malignancies bearing estrogen receptors. Nuclear binding has been demonstrated in endometrium, granulosa cells and breast cancer cells. DNA-incorporated ^{80m}Br has been shown to be radiotoxic, while unbound ^{80m}Br is not (36).

Howell *et al.* (37) have compared dose rate profiles for potentially useful radionuclides to be used for radioimmunotherapy. As one might expect, high-energy beta emitters such as ^{90}Y would be most effective for treating large tumors (>1 cm), whereas for small tumors (~ 1 mm), medium energy beta emitters are more suitable, while micrometastases may be best handled with low-energy electron emitters.

Woo *et al.* (38) have examined the effects of ^{125}I labeled monoclonal antibodies on cultured cancer cells. They have found that one of the antibodies tested is internalized by the cells and produces cytotoxicity as well as chromosomal damage. They assume that the internalized ^{125}I interacts with the cell nucleus. This type of immunoglobulin might be suitable for radioimmunotherapy with Auger-electron emitters.

Hou and Maruyama (39) have developed a complex of ^{111}In-bleomycin which binds to DNA and have augmented its cytotoxicity to small-cell lung cancer cells with hyperthermia. Baranowska-Kortylewicz *et al.* (40) have conjugated IUdR to immunoglobulins. The pyrimidine nucleoside-protein bond is hydrolyzed by lysosomal enzymes. This complex could be used to deliver the radioiodinated compound to specific tumor cells. Lastly, Goodman *et al.* (41) have begun a treatment protocol for brain tumors that involves IUdR infusion and brachytherapy. They plan to treat below and above the K absorption edge of iodine to test the effectiveness of photon activation therapy.

REFERENCES

1. K.F. BAVERSTOCK and D.E. CHARLTON, Eds. *DNA Damage by Auger Emitters.* Taylor and Francis, London, 1988.
2. A.R.S. YOUNIS and D.E. WATT, The quality of ionising radiations emitted by radionuclides incorporated into mammalian cells. *Phys. Med. Biol.* **34**, 821-834 (1989).
3. D.T. GOODHEAD, Spatial and temporal distribution of energy. *Health Phys.* **55**, 231-240 (1988).
4. J. BOOZ, H.G. PARETZKE, E. POMPLUN, and P. OLKO, Auger-electron cascades, charge potential and microdosimetry of iodine-125. *Radiat. Environ. Biophys.* **26**, 151-162 (1987).
5. A. HALPERN, Intra- and intermolecular energy transfer and superexcitation in post-Auger processes. *Radiochim. Acta* **50**, 129-134 (1990).
6. A.I. KASSIS, F. FAYAD, B.M. KINSEY, K.S.R. SASTRY, R.A. TAUBE, and S.J. ADELSTEIN, Radiotoxicity of ^{125}I in mammalian cells. *Radiat. Res.* **111**, 305-318 (1987).
7. E.M. LINK, I. BROWN, R.N. CARPENTER, and J.S. MITCHELL, Uptake and therapeutic effectiveness of ^{125}I- and ^{211}At- methylene blue for pigmented melanoma in an animal model system. *Cancer Res.* **49**, 4332-4337 (1989).
8. D.V. RAO, K.S.R. SASTRY, H.E. GRIMMOND, R.W. HOWELL, G.F. GOVELITZ, V.K. LANKA, and V.B. MYLAVARAPU, Cytotoxicity of some indium radiopharmaceuticals in mouse testes. *J. Nucl. Med.* **29**, 375-384 (1988).
9. J.R.N. McLEAN and D. WILKINSON, The radiation dose to cells *in vitro* from intracellular indium-111. *Biochem. Cell Biol.* **67**, 661-665 (1989).
10. J.R. McLEAN, D.H. BLAKEY, G.R. DOUGLAS, and J. BAYLEY, The Auger electron dosimetry of indium-111 in mammalian cells *in vitro. Radiat. Res.* **119**, 205-218 (1989).
11. J. BIALOBRZESKI, J. LINIECKI, J. GREGER, D. BRYKALSKI, and A. ZADROZNA, Radiation doses from ^{51}Cr-bleomycin. *Nuklearmedizin* **26**, 97-104 (1987).
12. M. VEZZA, D. GIULIANI, D.V. RAO, and B.S. MORSE, Chromium-51 dosimetry of lymphocytes labeled incidentally during nuclear medicine procedures. *Nucl. Med. Biol.* **14**, 75-77 (1987).

13. G.M. MAKRIGIORGOS, S.J. ADELSTEIN, and A.I. KASSIS, Limitations of conventional internal dosimetry at the cellular level. *J. Nucl. Med.* **30**, 1856-1864 (1989).
14. G.M. MAKRIGIORGOS, S. ITO, J. BARANOWSKA-KORTYLEWICZ, D.W. VINTER, A. IQBAL, A.D. VAN DEN ABBEELE, S.J. ADELSTEIN, and A.I. KASSIS, Inhomogeneous deposition of radiopharmaceuticals at the cellular level: Experimental evidence and dosimetric implications. *J. Nucl. Med.* **31**, 1358-1363 (1990).
15. G.M. MAKRIGIORGOS, S.J. ADELSTEIN, and A.I. KASSIS, Cellular radiation dosimetry and its implications for estimation of radiation risks: Illustrative results with technetium 99m-labeled microspheres and macroaggregates. *JAMA* **264**, 592-595 (1990).
16. D.E. CHARLTON and J.L. HUMM, A method of calculating initial DNA strand breakage following the decay of incorporated ^{125}I. *Int. J. Radiat. Biol.* **53**, 353-365 (1988).
17. P. UNAK and T. UNAK, Microscopic energy absorption of the DNA molecules from Auger electrons of iodine-125. *Appl. Radiat. Isot.* **39**, 1037-1040 (1988).
18. H.A. WRIGHT, R.N. HAMM, J.E. TURNER, R.W. HOWELL, D.V. RAO, and K.S.R. SASTRY, Calculations of physical and chemical reactions with DNA in aqueous solution from Auger cascades. *Radiat. Prot. Dosim.* **31**, 59-62 (1990).
19. E. POMPLUN, A new DNA target model for track structure calculations and its first application to I-125 Auger electrons. *Int. J. Radiat. Biol.* **59**, 625-642 (1991).
20. G.M. MAKRIGIORGOS, R.M. BERMAN, J. BARANOWSKA-KORTYLEWICZ, E. BUMP, J.L. HUMM, S.J. ADELSTEIN, and A.I. KASSIS, DNA damage produced in V79 cells by DNA-incorporated iodine-123: A comparison with iodine-125. *Radiat. Res.* **129**, 309-314 (1992).
21. R.F. MARTIN, G. D'CUNHA, M. PARDEE, and B.J. ALLEN, Induction of double-strand breaks following neutron capture by DNA-bound ^{157}Gd. *Int. J. Radiat. Biol.* **54**, 205-208 (1988).
22. R. NATH, P. BONGIORNI, and S. ROCKWELL, Enhancement of IUdR radiosensitization by low energy photons. *Int. J. Radiat. Oncol. Biol. Phys.* **13**, 1071-1079 (1987).
23. R.W. MILLER, W. DeGRAFF, T.J. KINSELLA, and J.B. MITCHELL, Evaluation of incorporated iododeoxyuridine cellular radiosensitization by photon activation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* **13**, 1193-1197 (1987).
24. D. LARSON, W.J. BODELL, C. LING, T.L. PHILLIPS, M. SCHELL, D. SHRIEVE, and T. TROXEL, Auger electron contribution to bromodeoxyuridine cellular radiosensitization. *Int. J. Radiat. Oncol. Biol. Phys.* **16**, 171-176 (1989).
25. K. TAKAKURA, Auger effects on bromo-deoxyuridine-monophosphate irradiated with monochromatic X-rays around bromine K-absorption edge. *Radiat. Environ. Biophys.* **28**, 177-184 (1989).
26. A.I. KASSIS, G.M. MAKRIGIORGOS, and S.J. ADELSTEIN, Implications of radiobiologic and dosimetric studies of DNA-incorporated ^{123}I: The use of the Auger effect as a biologic probe at the nanometre level. *Radiat. Prot. Dosim.* **31**, 333-338 (1990).
27. E. POMPLUN, J. BOOZ, A. DYDEJCZYK, and L.E. FEINENDEGEN, A microdosimetric interpretation of the radiobiologic effectiveness of ^{125}I and the problem of quality factor. *Radiat. Environ. Biophys.* **26**, 181-188 (1987).

28. D.V. RAO, V.R. NARRA, R.W. HOWELL, V.K. LANKA, and K.S.R. SASTRY, Induction of spermhead abnormalities by incorporated radionuclides: Dependence on subcellular distribution, type of radiation, dose rate, and presence of radioprotectors. *Radiat. Res.* **125**, 89-97 (1991).
29. J.M. WHALEY and J.B. LITTLE, Efficient mutation induction by ^{125}I and ^{131}I decays in DNA of human cells. *Radiat. Res.* **123**, 68-74 (1990).
30. J.M. WHALEY, A.I. KASSIS, B.M. KINSEY, S.J. ADELSTEIN, and J.B. LITTLE, Mutation induction by ^{125}Iodoacetylproflavine, a DNA-intercalating agent, in human cells. *Int. J. Radiat. Biol.* **57**, 1087-1103 (1990).
31. J.L. HUMM and D.E. CHARLTON, A new calculational method to assess the therapeutic potential of Auger electron emission. *Int. J. Radiat. Oncol. Biol. Phys.* **17**, 351-360 (1989).
32. J.L. HUMM, K.D. BAGSHAWE, S.K. SHARMA, and G. BOXER, Tissue dose estimates following the selective uptake of ^{125}IUdR and other radiolabelled thymidine precursors in resistant tumours. *Br. J. Radiol.* **64**, 45-49 (1991).
33. J. BARANOWSKA-KORTYLEWICZ, G.M. MAKRIGIORGOS, A.D. VAN DEN ABBEELE, R.M. BERMAN, S.J. ADELSTEIN, and A.I. KASSIS, 5-[^{123}I]Iodo-2'-deoxyuridine in the radiotherapy of an early ascites tumor model. *Int. J. Radiat. Oncol. Biol. Phys.* **21**, 1541-1551 (1991).
34. R.E. ANDERSON and J.A. HOLT, Binding of radiolabeled estrogens by human cells *in vitro*: Implications to the development of a new diagnostic and therapeutic modality in the treatment of malignancies with estrogen receptors. *Gynecol. Oncol.* **34**, 80-83 (1989).
35. E.R. DeSOMBRE, R.C. MEASE, A. HUGHES, P.V. HARPER, O.T. DeJESUS, and A.M. FRIEDMAN, Bromine-80m-labeled estrogens: Auger electron-emitting, estrogen receptor-directed ligands with potential for therapy of estrogen receptor-positive cancers. *Cancer Res.* **48**, 899-906 (1988).
36. E.R. DeSOMBRE, P.V. HARPER, A. HUGHES, R.C. MEASE, S.J. GATLEY, O.T. DeJESUS, and J.L. SCHWARTZ, Bromine-80m radiotoxicity and the potential for estrogen receptor-directed therapy with Auger electrons. *Cancer Res.* **48**, 5805-5809 (1988).
37. R.W. HOWELL, D.V. RAO, and K.S.R. SASTRY, Macroscopic dosimetry for radioimmunotherapy: Nonuniform activity distributions in solid tumors. *Med. Phys.* **16**, 66-74 (1989).
38. D.V. WOO, D. LI, L.W. BRADY, J. EMRICH, J. MATTIS, and Z. STEPLEWSKI, Auger electron damage induced by radioiodinated iodine-125 monoclonal antibodies. *Front. Radiat. Ther. Oncol.* **24**, 47-63 (1990).
39. D. HOU and Y. MARUYAMA, Enhanced killing of human small cell lung cancer by hyperthermia and indium-111-bleomycin complex. *J. Surg. Oncol.* **44**, 5-9 (1990).
40. J. BARANOWSKA-KORTYLEWICZ, S.J. ADELSTEIN, and A.I. KASSIS, 5-Iodo-2'-deoxyuridine-protein conjugates: Synthesis and enzymatic degradation. *Select. Cancer Ther.* **6**, 1-13 (1990).
41. J.H. GOODMAN, R.A. GAHBAUER, C. KANELLITSAS, N.R. CLENDENON, B.H. LASTER, and R.G. FAIRCHILD, Theoretical basis and clinical methodology for stereotactic interstitial brain tumor irradiation using iododeoxyuridine as a radiation sensitizer and ^{145}Sm as a brachytherapy source. *Stereotact. Funct. Neurosurg.* **54/55**, 531-534 (1990).