Biology Relevant to Space Radiation

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Introduction

The biological effects of the radiations to which the general and working populations on earth are exposed are becoming known with an increasing degree of detail. This knowledge is the basis of the estimates of risk (NCRP, 1983a; UNSCEAR, 1994) that, in turn, fosters a comprehensive and evolving radiation protection system (ICRP, 1990; NCRP, 1983b). The substantial body of information has been, and is being, applied to the questions about the biological effects of radiation in space and the associated risk estimates.

The purpose of this paper is not to recount all the biological effects of radiation but to concentrate on those that may occur as a result from exposure to the radiations encountered in space. In general, the biological effects of radiation in space are the same as those on earth. However, the evidence that the effects on certain tissues by the heaviest-charged particles can be interpreted on the basis of our knowledge about other high-LET radiation is equivocal. This specific question will be discussed in greater detail later.

It is important to point out that there are only very limited data of the effects on humans of two components of the radiations in space, namely protons and heavy ions. Thus, the

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predictions of effects on the crews in space are all based either: 1) on experimental systems exposed on earth at rates and fluences that are higher than those encountered in space or 2) on the effects of gamma or X rays with estimates of the equivalent doses using quality factors.

Factors That Influence the Biological Effects

Dr. Robbins has described the radiation environments and the component types of radiation, in particular protons and their secondaries, as well as the small but important component of GCR, namely heavy ions. The characteristics that are important to the understanding of their biological effects and the assessment of the risk are: 1) total doses that may be incurred on particular missions, 2) dose and fluence rates, 3) protraction, and 4) LET, energy, and track structure of the particles.

Total Dose

The factors that influence the total equivalent dose during mission in low-earth orbit are: 1) duration, 2) altitude, 3) orbital inclination, and 4) the shielding. In the case of deep space missions, the radiation from the sporadic solar particle events (SPE) must also be taken into account.

The total dose incurred on the US space missions have been low because, with the exception of Skylab, the durations of the missions have been short. In contrast, the exposure

during a three-year interplanetary mission could result in the accrual at a low-dose rate of an equivalent dose of about 1 Sv which is in excess of the limit recommended for the working lifetime of a radiation worker on earth. Both altitude and orbital inclination influence the amount and quality of the radiation, and shielding becomes increasingly important with the duration of the mission.

Biological Effects of Concern

In the context of this symposium, the biological effects of concern are those that pose a risk as a result of exposure to the radiation environments in space. The effects of concern for recommending radiation limits for the adventurers in space are considered under two categories, deterministic effects and stochastic effects. Radiation protection limits for terrestrial radiation workers are set at levels to prevent the occurrence of deterministic effects and to limit stochastic effects to what is considered an "acceptable" level. The selection of what is acceptable, is, of course, the subject of this symposium.

In the case of deterministic effects, it is the threshold dose that is important. For radiation protection purposes, threshold doses are those below which any effects that occur are either not easily detectable or are not of clinical significance. Threshold doses are significantly higher for almost all deterministic effects if the exposure is protracted, a possible exception being effects on the testes. For example, the equivalent dose limit recommended for protection against deterministic effects for exposures in low-earth orbit over a one-year period was 0.5 Sv

(NCRP, 1989) which translates into an equivalent dose rate of 9×10^{-7} Sv min^{-1}. The effect at such an equivalent dose rate is much less than an acute dose.

Acute deterministic effects, such as on the gastrointestinal tract resulting in nausea and vomiting and effects on the bone marrow, will not occur in either low-earth orbit or as a result of the ambient radiation in deep space. It is in the case of a large SPE that the possibility of acute effects must be considered. The total dose but particularly the dose and fluence rates determine the probability of the occurrence of acute deterministic effects.

Table 1

WHAT IS A LOW DOSE RATE?

NCRP (1980)	0.05 Gy y^{-1}
ICRP (1991)	0.1 Gy h^{-1}
	(876 Gy y^{-1})
UNSCEAR (1993)	0.1 mGy min^{-1}
	(52.56 Gy y^{-1})

Dose and Fluence Rates

The equivalent dose rates that will be experienced in low-earth orbit, while higher than on earth, are low. The highest rates are during the traversal of the South Atlantic Anomaly in which the dose rate of the protons may reach about 0.002 mGy min^{-1} at an altitude below 300 km. Integrated over a day the equivalent dose rate could be about 0.23 m Sv d^{-1}. Whereas, at greater than 600 km the daily rate could be about 1.6 mGy (Badhwar *et al.*, 1992).

The dose rate of the protons and the fluence rates of heavy ions in deep space are also at low-dose rates. The definition of low-dose rate varies as can be seen from Table I. There is a considerable diversity of opinion in what is a low-dose rate. This is, in part, because the committees opining on the question were considering different aspects. In Fig. I, one can see that, in the case of survival of clonogenic cells in the gut, there is a marked reduction in the cell killing at a dose rate of 7.2 Gy d^{-1}. The results of *in vitro* studies suggest the maximal effect of reducing the dose rate is reached at about 5.2 Gy d^{-1} (Bedford and Mitchell, 1973). However, in the case of life shortening, with exposures at low-dose rates at which the cause of life shortening is considered to be excess mortality from tumors, the dose rate at which the effect becomes dose-rate independent (slope 1 on the log-log scale for mortality rate as a function of radiation dose rate) is about 0.2 Gy d^{-1} or 73 Gy y^{-1}. Based on this result, the UNSCEAR (1993) choice of 0.1 m Gy min^{-1} or about 53 Gy y^{-1} seems reasonable when stochastic effects are being considered. The unanswered, but very important, question is what should be the dose-rate

effectiveness factor at such dose rates for radiation protection. ICRP (1990) chose a factor of two for stochastic effects but did not select a factor for deterministic effects.

The effect of dose rate is, of course, important in estimating the risks of both the stochastic and deterministic effects. In low-earth orbit all radiations are at a low-dose rate. In deep space the only occasion in which a potential exists for exposure at a high-dose rate is at the peak of a very large SPE. The radiation in an SPE is almost entirely protons varying greatly in energy. It is assumed that the biological effects of protons are reduced at low-dose rates to a similar degree as that found for gamma rays.

On long-duration missions, not only will the dose rates be low, but the irradiation will be protracted over long periods, and the total dose becomes a prime consideration (Carnes and Fritz, 1991). The influence of total dose has been seen in survival of cells *in vitro* (Bedford and Mitchell, 1973) and in the induction of thymic lymphoma (Ullrich and Storer, 1979). In both cases the effect increased when a specific dose was reached.

It is not known what the maximum dose rate could be in the most intense particle events that might occur on a three-year-long mission to Mars. The analysis of Simonsen *et al.* (1991), based on the SPE in October 1989 (Fig. 2), suggests that with 10.0 g/cm^2 of shielding the peak dose rate could have reached about 0.4 Sv d^{-1} but for less than a day. These results suggest that even in the case of a very large SPE that with a level of shielding that is feasible, the dose rates in a space vehicle will be low in particular for deterministic effects. Many of the predictions of

the severity of the effects of SPEs appear to have been based on the assumption that the exposures would be at a high-dose rate and, thus, overestimated the risk of acute effects. However, better estimates of both the total doses and the dose rates that might be experienced in the worst-case SPE are needed. Similarly, better estimates of the effects of dose rate on the relevant biological effects, such as damage to skin, gut, and marrow, should be obtained.

The contribution of one large SPE to the risk of stochastic effects, while undesirable, will not be large in comparison to the potential total dose on a mission of long duration.

The Relationship of Radiation Quality and Biological Effects

The assessment of the biological effects of the radiation environment in deep space is complicated by the complexity of the types of radiation. Both the spectra of energies and of LETs are very much broader than in the terrestrial radiation environment. The biological effects are dependent on the energy, LET, and track structure.

It is a tenet of radiobiology, at least as it is applied to radiation protection, that the effects of different types of radiation are qualitatively alike and only quantitatively different. This is assumed to hold for both deterministic and stochastic effects. However, there are a number of significant differences between the effects of high-LET radiations and other types of radiation. These differences become marked when heavy-charged particles of LETs of the order of about 30 keV/μm and greater are considered. That the residual damage to DNA is different with very

high-LET radiations, such as alpha particles or iron ions compared to gamma rays, is not surprising when the density of ionization is considered (Fig. 3). Not only is the spectrum of DNA lesions, which is so important in determining the occurrence and nature of chromosome aberrations and mutation, different (Ward, 1994; Rydberg *et al.*, 1994), but the ability to repair efficiently and without error also changes with LET (Ritter *et al.*, 1977). As can be seen in Fig. 4, although the RBEs for DNA double-strand breaks determined by hybridization to 3.2 Mbp NotI fragments decrease with LET, the RBE for cell inactivation increases (Rydberg *et al.*, 1994). The explanation appears to lie in the fact that the clustering of DNA damage, which increases with LET, results in an increase in the time required for repair and in the frequency of errors in the repair.

The relative frequencies of different types of DNA damage and of different types of mutation are LET-dependent. However, apart from the identification of a specific mutation in *p53* induced by UV radiation (Brash *et al.*, 1992), specific mutations induced by radiation have not been identified unequivocally. The search for signature lesions continues.

The RBE for cell inactivation *in vitro* and for deterministic effects *in vivo* involving cell killing increase with LET reaching a peak of about 2 at about 100 keV/μm (Fig. 5). In proliferative tissues the loss of proliferative capacity explains the relationship of LET to RBE. In the case of tissues with a large population of cells that do not divide, such as the CNS, acute effects should be minimal with low doses of protons unless interphase death is more frequent than currently assumed. Since the dose rate of the protracted exposures to protons either in

low-earth orbit or in deep space is low, the deterministic effects with the total doses that are envisaged should not be a limiting factor.

In the case of heavy ions, there is much less known about the risk of either acute or late effects. Since the fluence rates are low, in particular of the particles of the higher Zs and energies, acute deterministic effects will not occur. Late deterministic effects are another matter. For example, 1) will there be a significant level of residual damage resulting in an age-related loss of neurons and 2) does the nature of the particle track with a distribution of energy deposition quite distinct from that of other types of radiation (Fig. 6) determine the occurrence and severity of late occurring effects? Little is known of the late effects on the CNS, but results suggest that late break down of DNA may occur (Williams and Lett, 1994, 1996). Results also suggest that heavy ions can cause neurochemical changes and alterations in behavior at relatively low doses (Rabin *et al.*, 1994).

Protons and HZE particles

Deterministic Effects

The available data for RBE values for protons while restricted to energies of 200 MeV and less does cover DNA damage, mutations, tumor induction, and deterministic effects on tissues in experimental animals. The data indicate that the RBEs are close to 1 relative to gamma rays. The experience with radiotherapy with protons suggests that an RBE of about 1 is

Table 2
TOTAL DOSES THAT CAUSE PERMANENT STERILITY IN WOMEN WITH MULTIPLE EXPOSURES

(From Ash 1980, Damewood and Grochow 1986)

Dose	15-40 y of Age	Over 40 y of Age
0.6	"No Effect"	"No Effect"
1.5	"No Effect" in Most Women	Some Risk of Sterilization
2.5 - 5.0	About 60% Permanently Sterilized	—
>8.0	Nearly 100% Permanently	

reasonable for acute effects on normal human tissues. This means that the probability of risk of deterministic effects of protons can probably be based on the data for such effects caused by gamma rays.

There are two effects that may occur with accrual of sufficient levels of proton radiation, namely, effects on fertility and cataract induction. In contrast to other biological effects, protraction of the exposure does not reduce and may increase the effect on fertility in the male. Temporary reduction of the production of sperm can occur with relatively low doses (Fig. 7), and with increasing doses the time required for recovery increases (see Meistrich and van Beck, 1990). The best estimates of the risk of sterility in women are shown in Table 2. It should be noted that the estimates are based on fractionated doses for radiotherapy and may overestimate the effects of protracted low-dose-rate exposures.

Cataract induction in humans has been studied in both radiotherapy patients (Merriam and Focht, 1957; Merriam *et al.*, 1972) and atomic bomb survivors (Otake and Schull, 1990). Assuming that the influence of fractionation and dose rate on the effects of proton radiation is comparable to that of gamma rays, the cataractogenic dose would be 4 Sv or more. The studies on monkeys exposed to single doses of protons (Lett *et al.*, 1991) suggest that doses below 2 Gy do not induce cataracts that would limit vision significantly. Since there are no data for cataract induction in humans by heavy ions, risk estimates must be extrapolated from animal studies. High RBE values have been reported for neutrons (Otake and Schull, 1991; Worgul *et al.*, 1996). In the case of heavy ions, Merriam *et al.* (1984) reported an RBE of 40 at 0.05 Gy for ^{40}Ar ions, and Brenner *et al.* (1991) suggest from their analysis of these data that a quality factor

of 50 would be more appropriate than 20 for heavy ions. Subsequent data for the effect of iron ions substantiates the high RBE at a dose 0.01 Gy (Brenner *et al.*, 1993). Unfortunately no estimate of the number of cells traversed by such a low fluence are given. Clearly the number of potentially abnormal lens fibres must be low.

There is some risk of some degree of lens opacification occurring as the result of the exposure that could occur on a Mars mission. However, the lesion would probably not interfere with vision significantly much before age-related cataracts are likely to occur.

Stochastic Effects

The effectiveness of protons in the induction of cancer in humans is not known, but based on data from monkeys (Wood, 1991), rats (Burns *et al.*, 1975, 1989), and mice (Clapp *et al.*, 1974), it is reasonable to assume that risk estimates for gamma irradiation can be applied. Therefore, risk estimates based on the data from atomic bomb survivors adjusted with an appropriate dose-rate effectiveness factor are considered applicable. In the case of heavy ions, the problem of estimating the probability of cancer induction is more complex. Not only are there no data for the induction of cancer in humans by any heavy ion, there are data for only one experimental animal system (Alpen *et al.*, 1994).

To use the cancer induction data obtained from populations exposed to low-LET, radiation quality factors (Q) for the spectrum of heavy-charged particles must be applied. Theoretically, an average Q can be obtained by integration of the relationship of Q to LET. In 1990, ICRP modified this relationship from that recommended in 1977 (Fig. 8). The two

important changes were: 1) the Q increased somewhat more steeply and reached a maximum of 30 at 100 keV/μm compared to 20 in the 1977 version and 2) in contrast to the curve proposed in 1977, which reached a plateau of 20 at about 100 keV/μm that extended over the higher range of LETs, the curve proposed in 1990 descended from the peak reaching a Q of about 10 at 1000 keV/μm. This latter part of the curve is described by the expression $300/\sqrt{L}$.

The only data that address the questions of the Q-L relationship for radiation >100 keV/μm are those for the induction of tumors of the Harderian gland (Figs. 9 and 10). It can be seen that the effectiveness increases when the prevalence of tumors is plotted as a function of LET or fluence, reaching a maximum of about 30 at about 100 keV/μm (Fig. 9) and a fluence between $5x10^{-2}$ to $1x10^{-2}$ particles/μm^2. There is no evidence, as yet, in this tumor system that the effectiveness decreases significantly at LETs considerably greater than 100 keV/μm. These results are in contrast to the ICRP (1990) Q-L relationship. There is a need for data for the induction of tumors in other and more representative tissues.

Whether absorbed dose, quality factor, and equivalent dose are the appropriate approach has been called into question (Bond *et al.*, 1985; Zaider and Brenner, 1985). Curtis *et al.* (1992, 1995) suggested using risk cross sections for estimating the risk of cancer induction by galactic cosmic rays. The risk cross section is defined as the probability per unit fluence of a particle of a particular type and energy, or LET, to induce a specific cancer. Figure 10 illustrates the type of data that is required. Since risk cross sections for different types of radiation are not yet known for representative types of cancer, quality factors still have to be used.

Conclusion

On missions of long duration in both low-earth orbit and deep space, acute effects are not of concern with the exception of exposure to astronauts who are not protected by shielding of the space vehicle or shielding on, say, the surface of the moon. Warning systems, mission management, and shielding should preclude the likelihood of what has been termed a "show stopper" event. Estimates of the danger that large SPEs pose do not appear to have taken into account the dose-rate effect. However, better information about the dose, dose rate, and the energy and LET spectra of the radiation at the organ level is required for planning of the necessary shielding.

Estimates of the late effects can be made, but the uncertainties are high because of lack of knowledge of both the stochastic and deterministic effects of heavy ions. Currently, stochastic effects at low-dose rates are considered to be a factor of about 2 less than the effects at a high-dose rate. It is important to establish the difference in the effect of prolonged protraction of exposures from the effect on acute high-dose-rate exposure so that a more accurate adjustment for the low-dose rates of space radiation can be made.

The question that is pertinent to the aims of this symposium is can we determine the risks sufficiently well to address the question of whether the risk is acceptable? The answer is yes, but to do so, some well-directed research is required to determine the effects of heavy ions.

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Figure Legends

Fig. 1 Left-hand panel. Clonogenic cells in the crypts of liberation in the small intestine per circumference of histological cross sections of the gut as a function of dose at 7.2 Gy d^{-1}, 65 Gy d^{-1}, and 518 Gy d^{-1} (Fu and Phillips, 1975).

Right-hand panel. Mortality rate of mice as a function of daily (10-11 h) dose rate on a log-log plot. The arrow indicates the approximate dose rate below which the life shortening becomes independent of dose rate and is dependent on total dose. This is the interpretation of the change from a slope=1 is that of 2 at the higher dose rates (Sacher and Grahn, 1964).

Fig. 2 The equivalent dose rate is shown as a function of time after the onset of the solar particle event that occurred in October 1989 assuming a shielding of 0.5 g/cm^2 al and 10.0 g/cm^2 al (Simonsen *et al.*, 1991).

Fig. 3 Schematic of DNA showing the ionization density for high-LET radiation (dense) and low-LET radiation (sparse) and the possible types of damage that radiation can induce.

Fig. 4 Cell inactivation of human fibroblasts as a function of the dose of x rays and 600 MeV/n iron. The RBEs for DNA double-strand breaks and inactivation for x rays neon and iron ions are shown. Data from Rydberg *et al.*, 1994.

Fig. 5 The RBE for cell inactivation of clonogenic cells in the testis as indicated by loss of weight in the spleen as indicated by the assay of CFUS and in the gut assayed by determination of crypt microcolonies as a function of LET (keV/μm). Redrawn from Ainsworth, 1986.

Fig. 6 Schematic to illustrate the difference in the deposition of energy at the tissue level between a low dose of low-LET radiation and two types of high-LET radiation, 1 meV neutron, and an iron particle.

Fig. 7 The percentage azoospermia in men as a function of: a) single dose of x rays; ● and Λ— and fractionated gamma rays; □. Data from Meistrich and Ven Beek (1990).

Fig. 8 Quality factor as a function of LET (keV/μm) proposed by ICRP 1977; ●●●●● and 1991; —. Curtis, personal communication.

Fig. 9 RBE as a function of LET (keV/μm) for induction of Harderian gland tumors in mice. Data from Fry *et al.*, 1985 and Alpen *et al.*, 1994.

Fig. 10 Proportion of mice with Harderian gland tumors as a function of fluence, particle/μm^2 the types of radiation indicated on the figure. Data from Alpen *et al.*, 1994.

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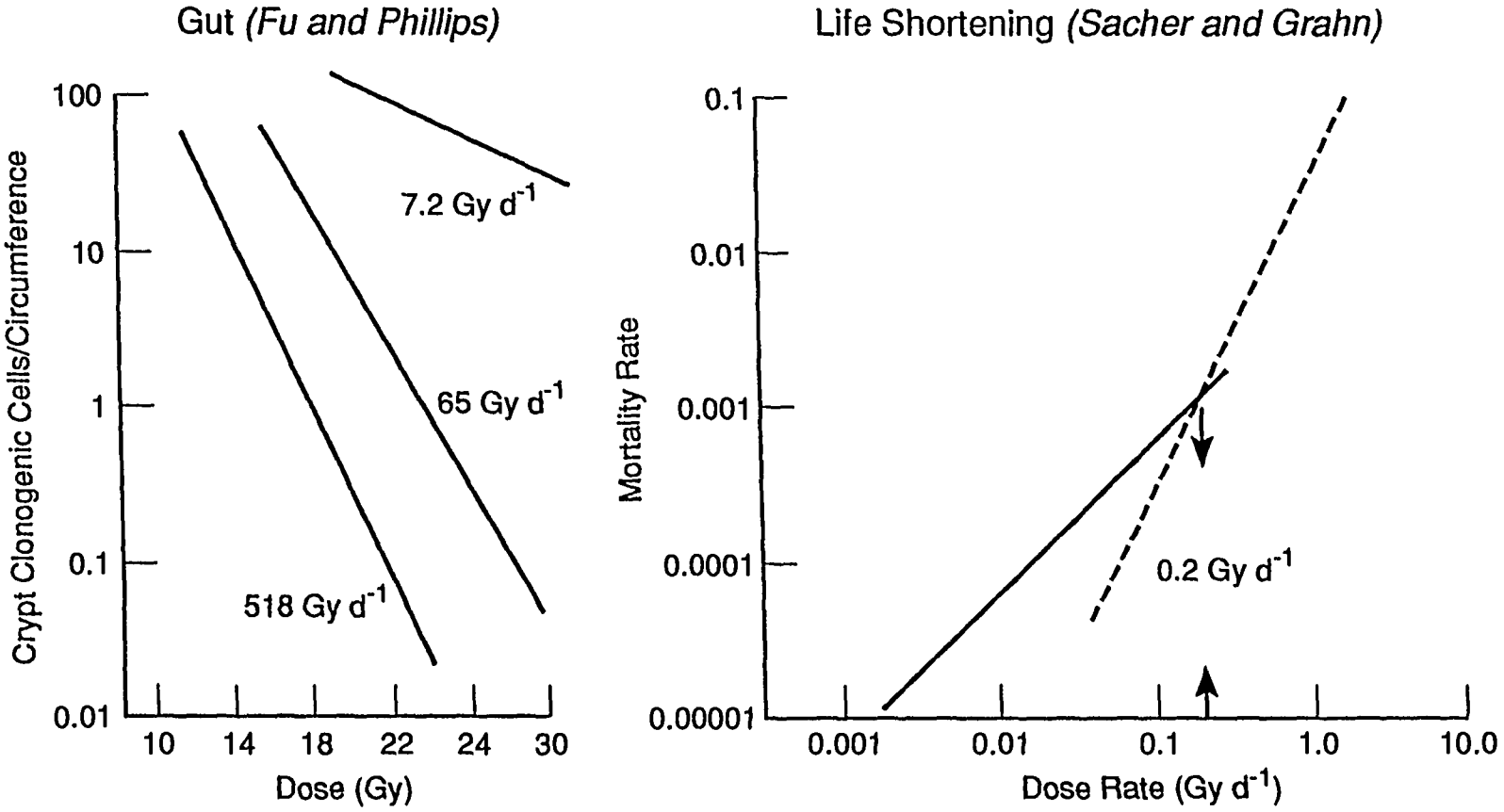
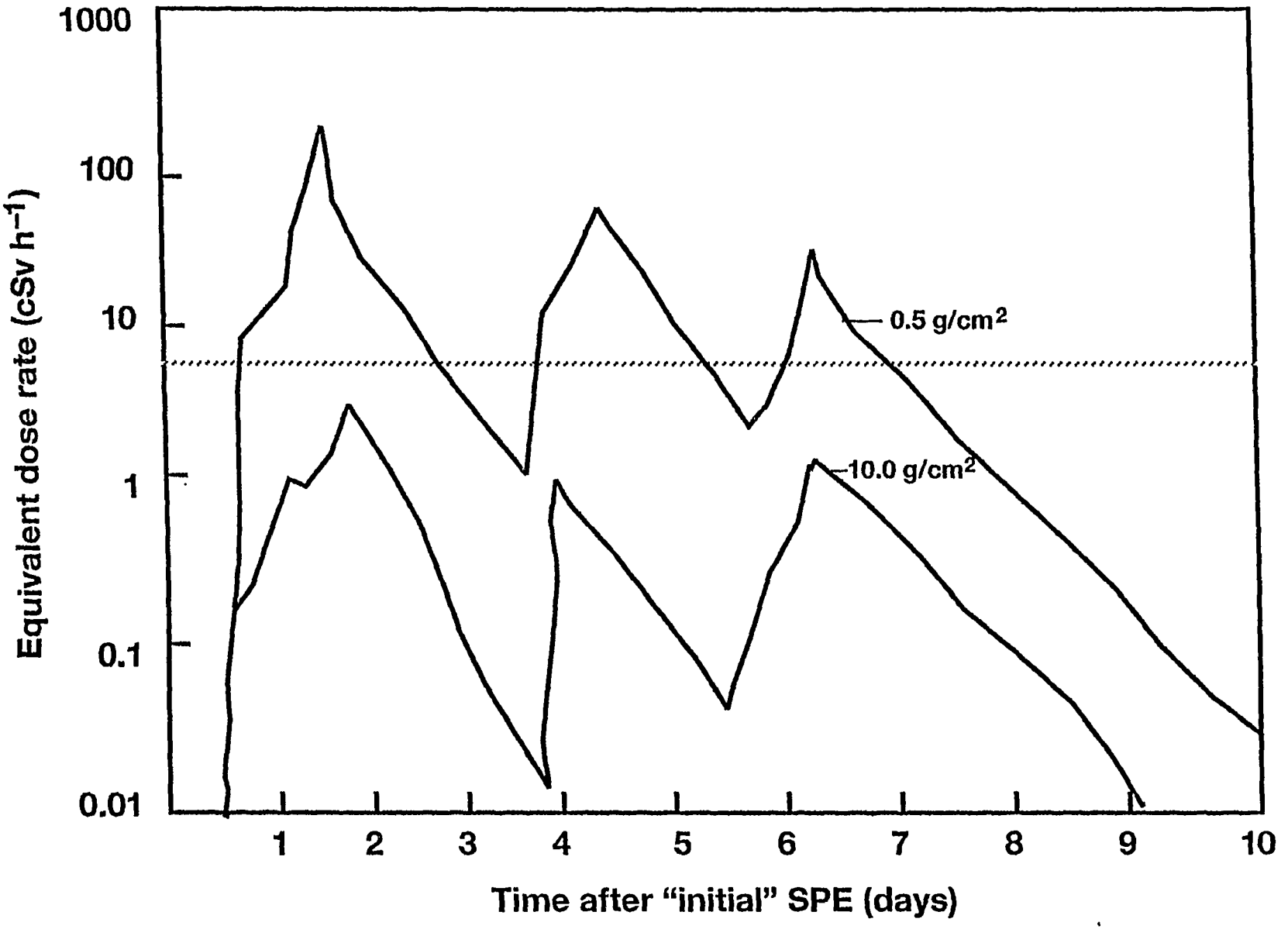
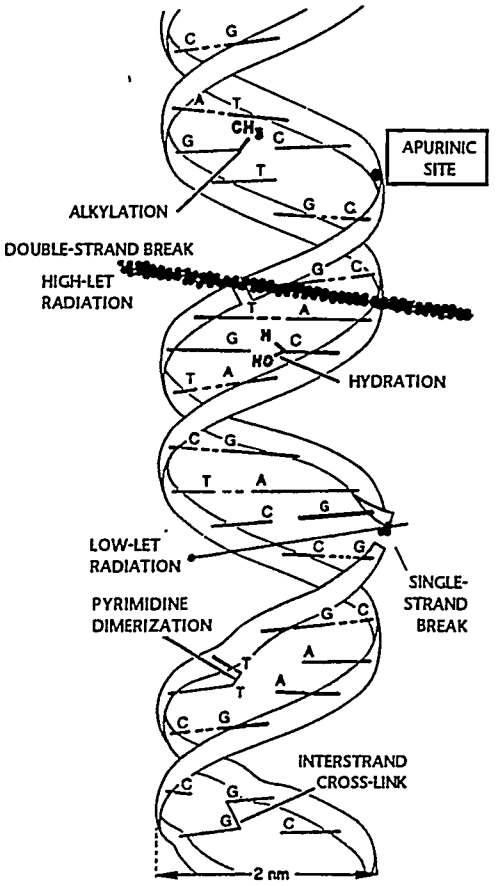
Dose Rate Effects



Low Dose Rate *(UNSCEAR 1993)*
0.14 Gy d^{-1}

Equivalent Dose Rate to the Skin Based on October 1989 SPE (Adapted from Simonsen *et al.*, 1991)

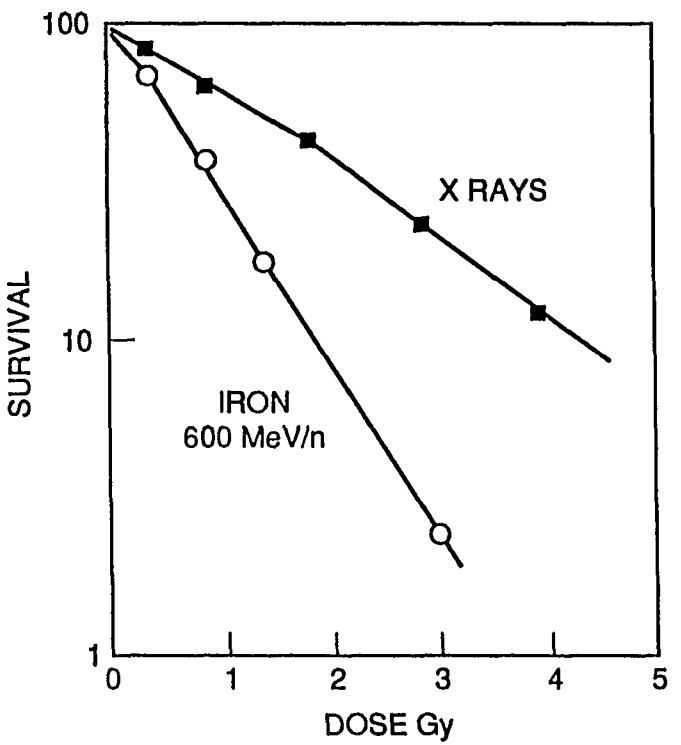



APURINIC SITE
ALKYLATION
DOUBLE-STRAND BREAK
HIGH-LET RADIATION
HYDRATION
LOW-LET RADIATION
SINGLE-STRAND BREAK
PYRIMIDINE DIMERIZATION
INTERSTRAND CROSS-LINK
2 nm

Cell Inactivation (*Rydberg et al.* 1994)

RBEs for Double Strand Breaks

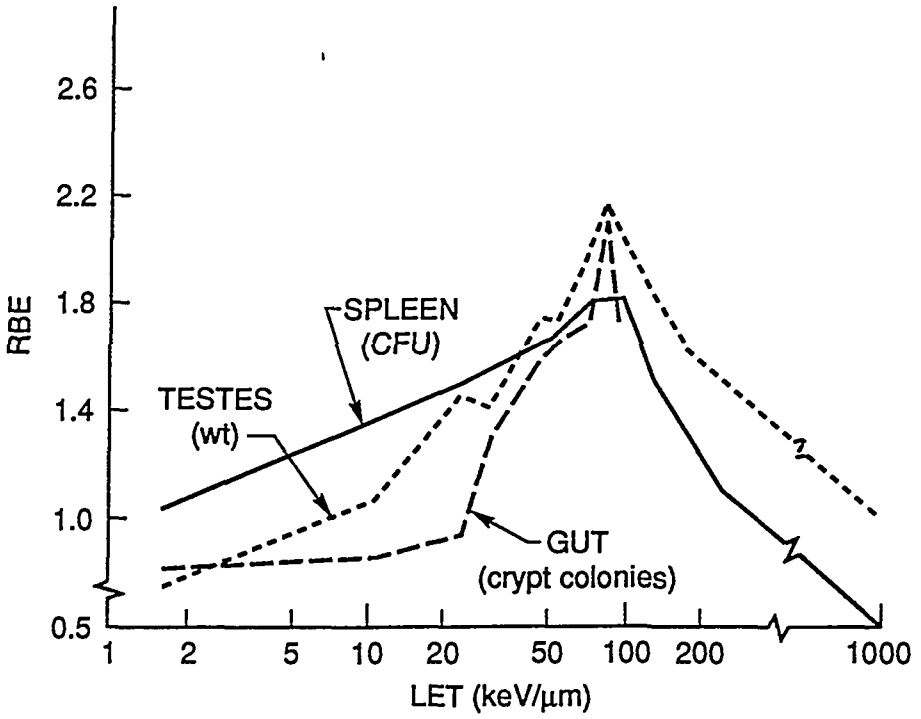
X rays	1.0
Neon (32 keV/μm)	0.85
Iron (190 keV/μm)	0.55



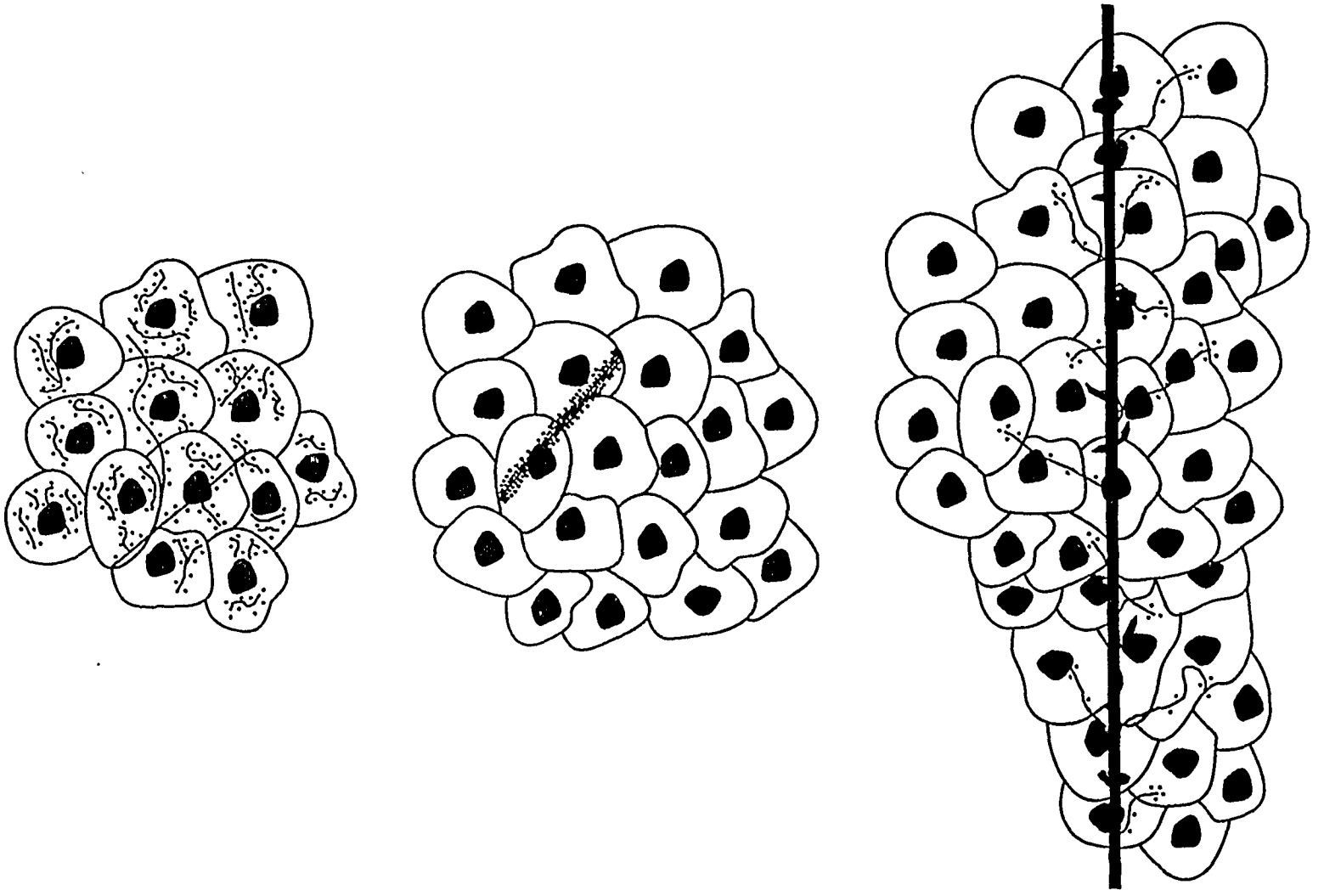
RBEs for Cell Inactivation (D_{10} values)

X rays	1.0
Neon	1.26
Iron	2.4

Deterministic Effects
Cell Inactivation: Normal Tissues



DEPOSITION OF RADIATION ENERGY

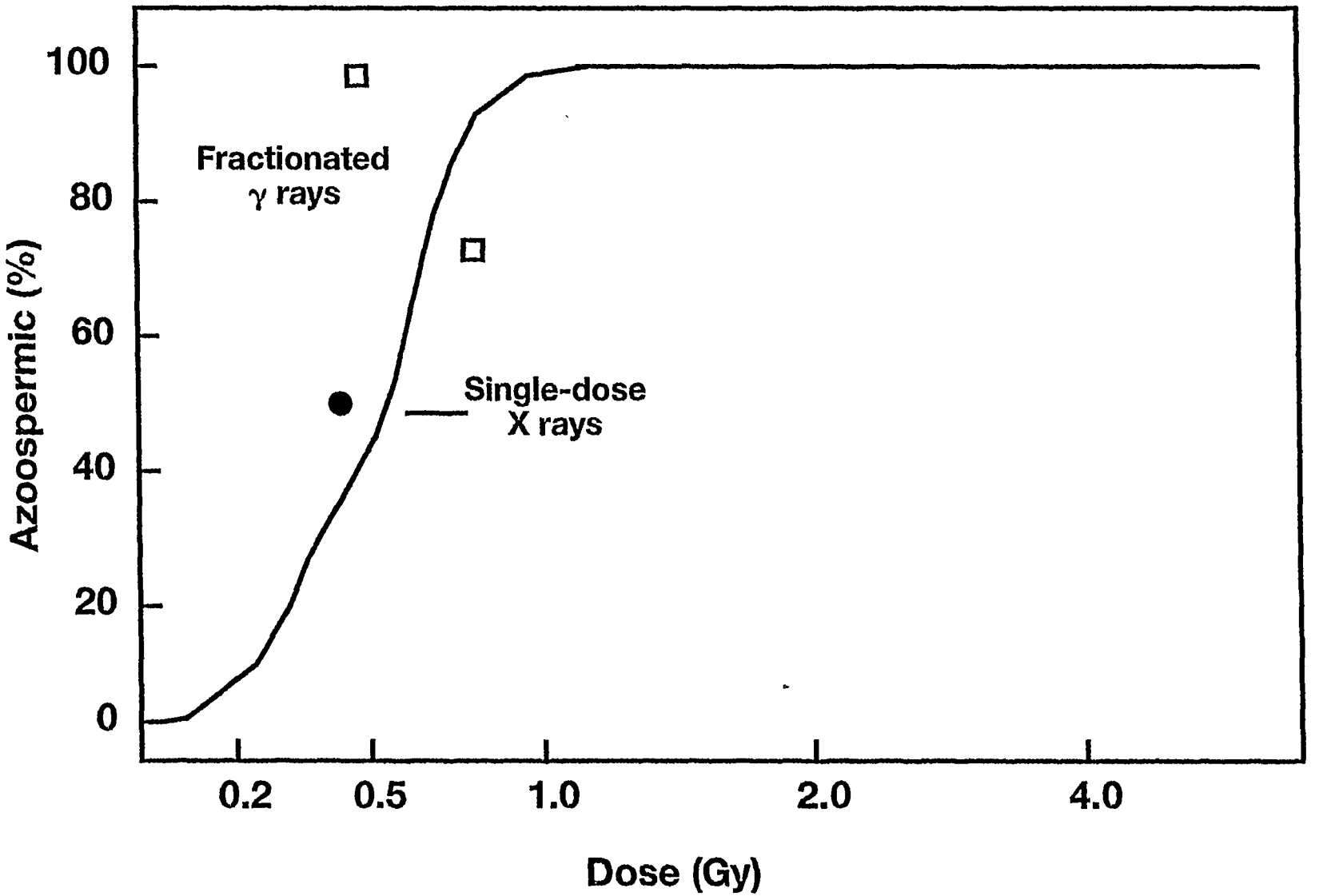


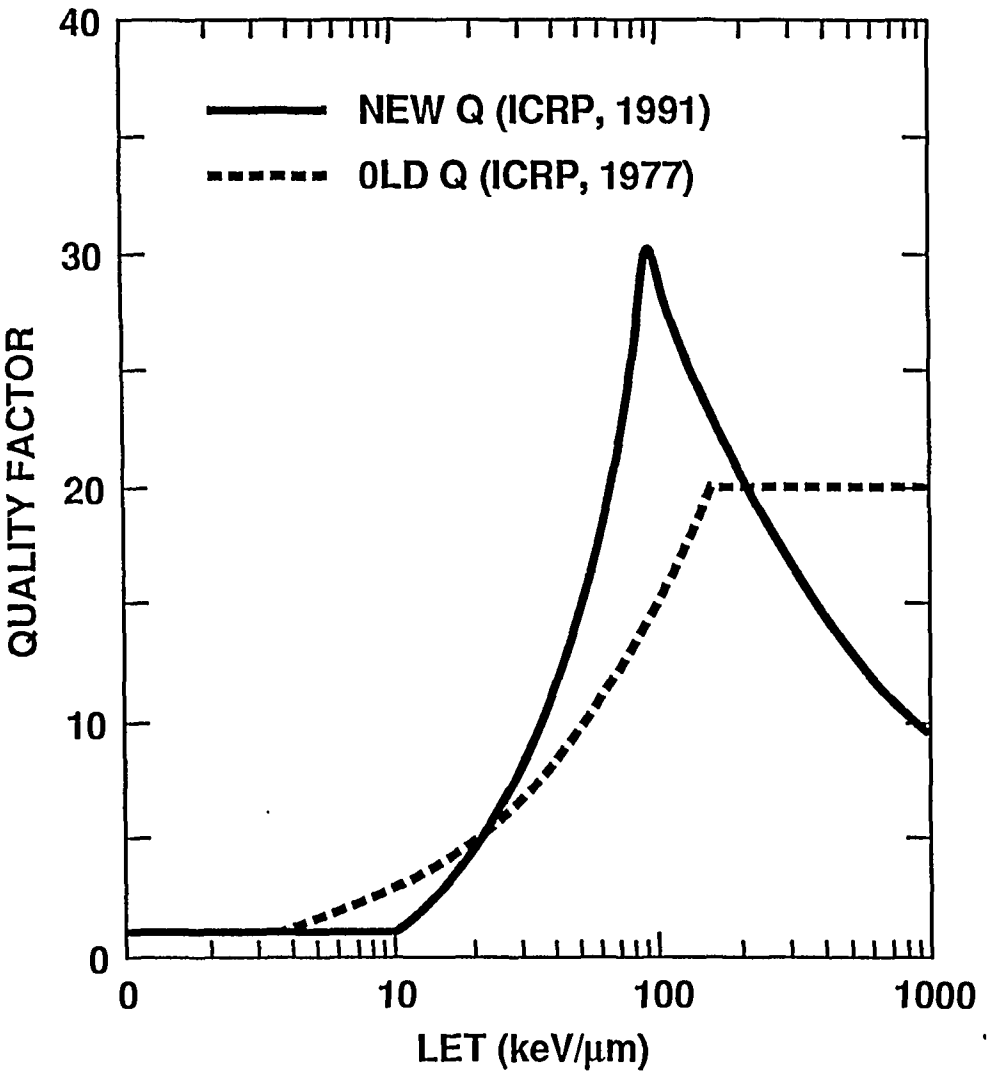
1 cGy
1 MeV GAMMA RAYS
~4 TRACKS/CELL

1 cGy
1 MeV NEUTRONS
~1 TRACK/20 CELLS

1 PARTICLE TRACK
Fe (z = 26)
MANY CELLS/TRACK

Radiation Sensitivity of Human Testis
(from Meistrich and van Beek, 1990)





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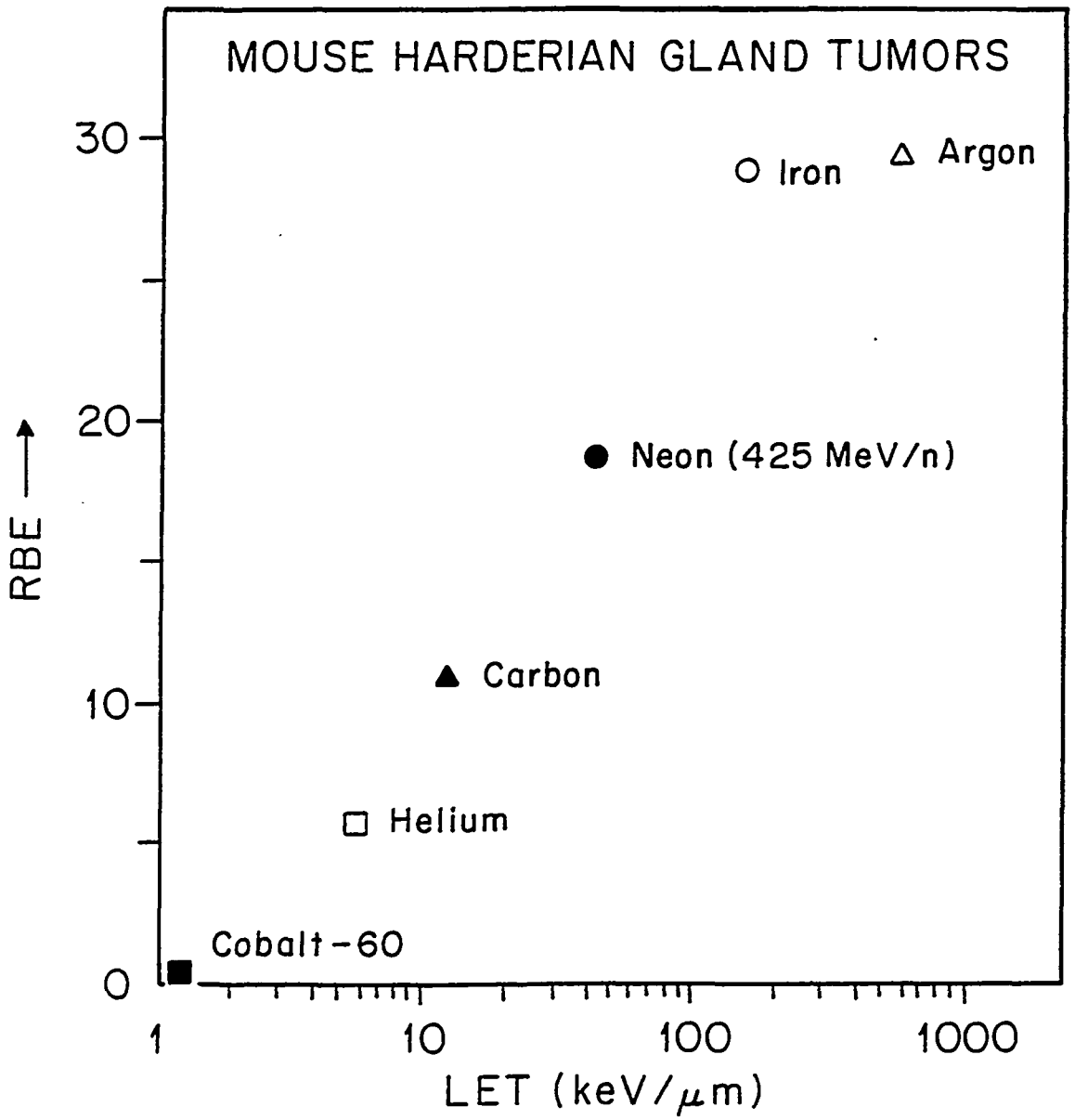
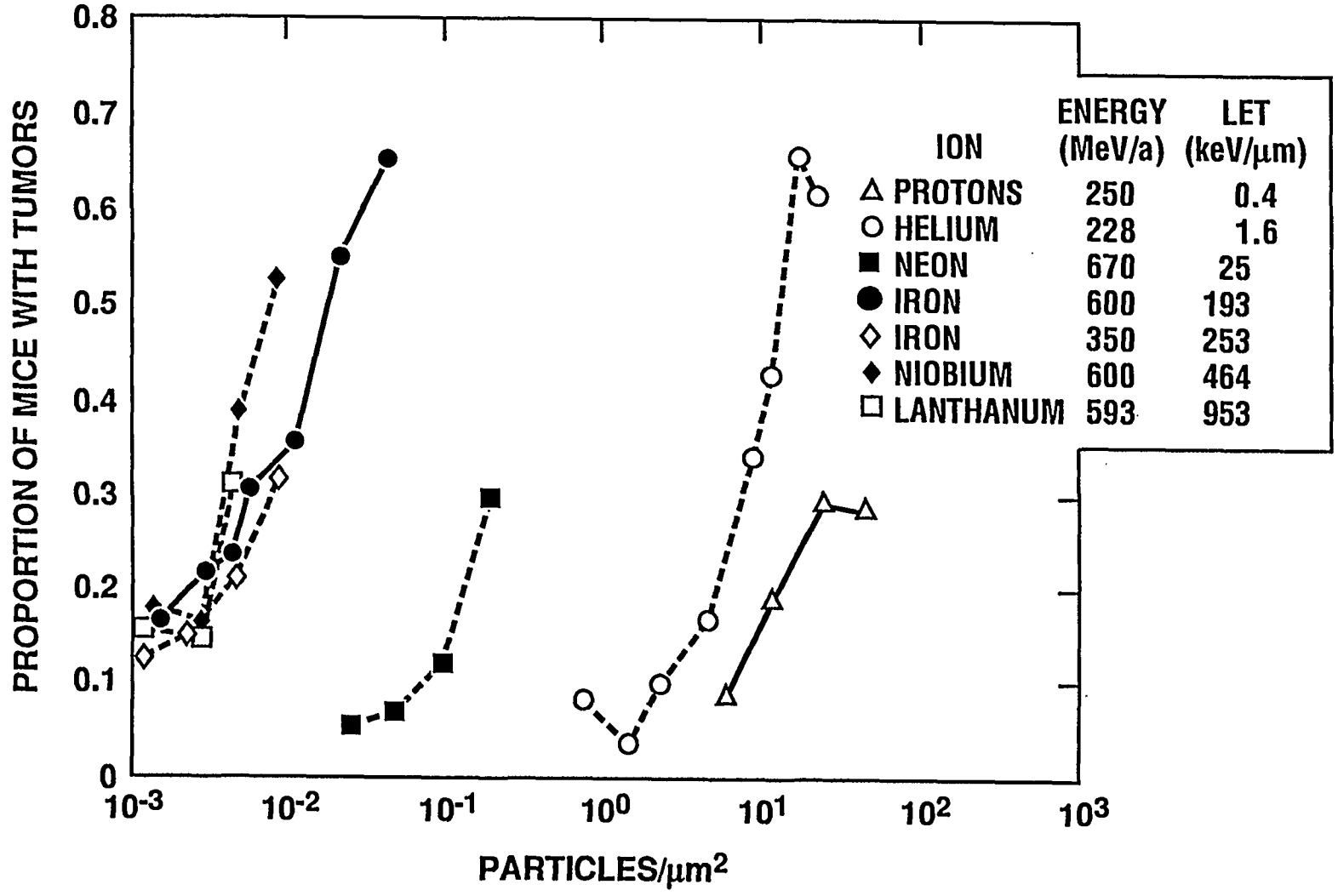

MOUSE HARDERIAN GLAND TUMORS
30
20
10
0
RBE
Iron
Argon
Neon (425 MeV/n)
Carbon
Helium
Cobalt-60
1
10
100
1000
LET (keV/μm)



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