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The initial physical damage produced by ionizing radiations†

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Biophysical studies of different ionizing radiations and their differences in biological effect can provide useful information and constraints on the nature of the initial biologically relevant damage and hence the subsequent biochemistry and repair processes. It is clear that the nature of the predominant critical component produced by densely ionizing (high-LET) radiations is qualitatively, as well as quantitatively, different from that which predominates for low-LET radiations. Comparisons of radiation track structure with observed biological effects of the radiations allow hypotheses to be developed as to the nature of these different types of damage. That associated with low-LET radiations seems consistent with what is known about DNA double-strand breaks (dsb). It is produced predominantly by a localized cluster of ionizations within a single electron 'track end' either by direct action on the DNA or in conjunction with closely-associated molecules. The characteristic high-LET damage is somewhat larger in number of ionizations and spatial extent and therefore presumably also in molecular complexity. It is suggested that the total spectrum of initial damage be categorized into four classes; in addition to the above two this would include on the one extreme sparse isolated ionizations, which may lead to very simple products that are of limited biological relevance, and on the other extreme very large and relatively rare events which are uniquely achievable by some high-LET radiations, such as alpha-particles, but not at all by low-LET radiations. These biophysical considerations pose a challenge to radiation chemistry studies to consider the chemical consequences of highly localized clusters of initial ionizations and excitations in or very near to DNA, and to biochemistry to consider classes of damage involving DNA (and perhaps associated molecules) of greater complexity than the simplest dsb.

1. Radiation damage—general considerations

In considering relevant damage produced by ionizing radiations in DNA in mammalian cells a number of factors should be recognized which clearly distinguish ionizing radiations from other DNA-damaging agents. Of central importance is the fact that the radiation insult is *always* in the form of highly structured tracks which contain a diversity of microscopic features. Most DNA will not receive a direct interaction from the radiation, nor will the closely adjacent material. By contrast those portions in (or near to) which there is an interaction may have received anything from a small amount of energy (say a single ionization or excitation) up to quite large amounts (at least some tens of ionizations and excitations even for the least densely ionizing radiations). For small target volumes the insults, when they do occur, will almost invariably be due to individual radiation tracks alone, because the probability of tracks overlapping is negligible even at high doses of tens or hundreds of grays.

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Figure 1 provides simple schematic illustrations of radiation tracks passing through a cell nucleus. Some typical features of the tracks are displayed for radiations of low linear energy transfer (LET). In all cases the radiations can produce a wide spectrum of patterns and magnitudes of local energy deposition in DNA or associated molecules. A notable feature of low-LET radiations is that most of the energy is deposited in the form of single isolated sparse ionizations or excitations; nevertheless there is a substantial component of very localized clusters which occur predominantly near the terminal 'track-ends' of low-energy secondary electrons. Low-energy electrons of $\lesssim 5$ keV are responsible for a significant (30–50 per cent) part of the local energy deposition by *all* low-LET radiations (figure 2).

The importance of the microscopic features of radiation tracks is enhanced by the experimental evidence which now shows that reactive radiolysis products, such as hydroxyl radicals, are unlikely to diffuse more than a very small distance (a few

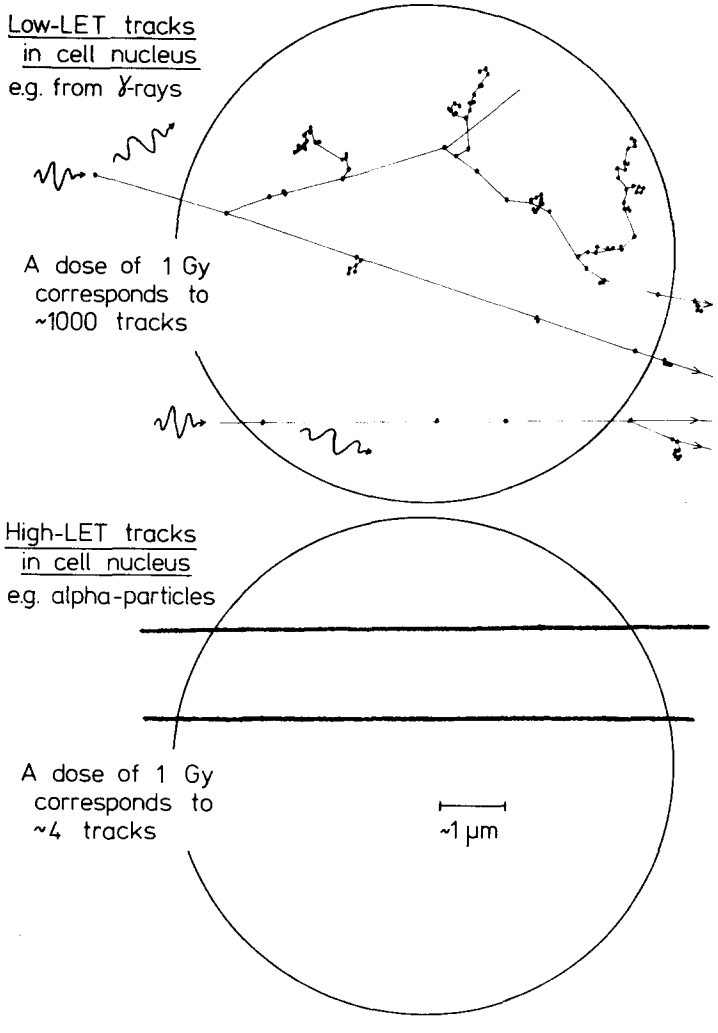

Figure 1. Schematic representation of tracks from low-LET γ-rays or high-LET α-particles passing through a cell nucleus. (Reproduced from Goodhead 1988.)

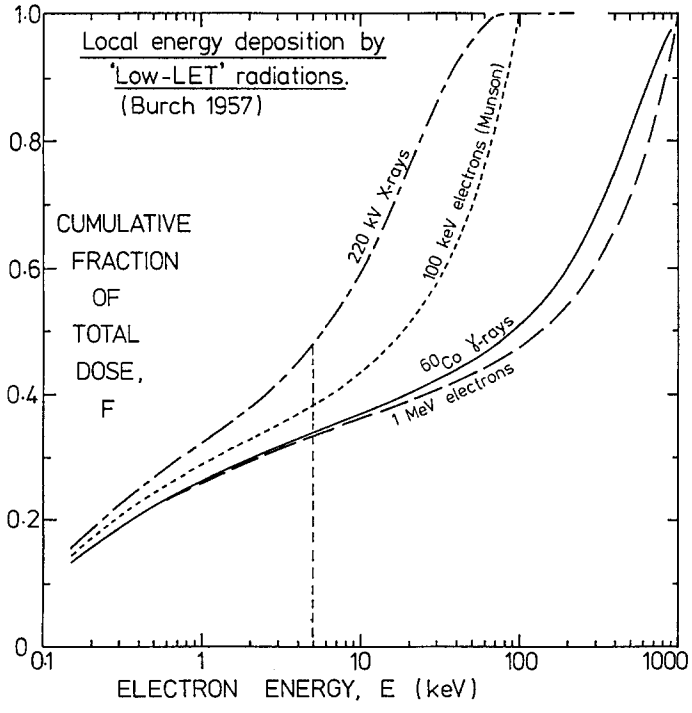

Figure 2. Fractions of dose from low-LET radiations which are deposited locally by electrons of different energies in the equilibrium slowing-down spectrum. (Plotted from calculations of Burch 1957; any energy transfer, to an atom or secondary electron, of energy <100 eV is regarded as local.) Reading from the vertical line shows that low-energy electrons of $\lesssim 5$ keV contribute ~ 30–50 per cent of the total absorbed dose. Modern interaction-by-interaction Monte Carlo track simulations (Paretzke 1987) indicate that the Burch calculations slightly *under*estimate the true contribution from low energy electrons (H. Nikjoo, personal communications).

nanometres) in mammalian cells (Roots and Okada 1975, Chapman and Gillespie 1981) because of the very highly scavenging nature of the intracellular environment. Therefore damage to DNA should be determined by the very local properties of the individual radiation tracks within the DNA itself, or in very closely adjacent molecules—which may include protein and bound water.

The wide spectrum of initial local physical damage produced by radiation should lead to a wide spectrum of chemical reactions and DNA damage. Part of this spectrum is demonstrated by the range of damage seen in biochemical assays, such as base damage, single-strand breaks (ssb), double-strand breaks (dsb) and cross-links. The full variety is probably greatly masked by the methods of assay, which are usually unable to distinguish further degrees of complexity; for example, dsb are usually grouped into a single class irrespective of the nature of the breaks or associated damage.

The spectrum of initial damage is further revealed by the clear qualitative, as well as quantitative, differences between the damage which is predominantly responsible for effects of low-LET radiations as compared to high-LET radiations. Many factors can intervene to modify the probabilities with which the initial low-LET damage leads to final cellular effect. Such factors include dose fractionation,

dose rate, oxygenation, delayed plating, sensitizers and protectors. Their influence on the outcome of the dominant initial damage from high-LET radiations is small or absent, especially in the case of narrow, densely ionizing tracks without long-range low-LET-like delta-ray electrons. Therefore there must be a clear qualitative difference from the earliest stages between these two classes of damage which originate from the different microscopic properties of the tracks. Simple biochemical assays may not distinguish between these classes of damage, although they may be partially revealed by differences in the kinetics or proportions of damage repaired.

The importance of the initial physical structure of the radiation tracks is further revealed by the general observation that, with few exceptions, the efficiency of a given dose of different radiations in producing a wide variety of cellular effects increases when the ionization density of the tracks increases. Thus it has been found in most studies that slow α-particles are more efficient than electron track-ends which are in turn more efficient than γ-rays, for the same absorbed dose (Goodhead *et al.* 1985). From this we may infer that clustering of atomic damage (ionizations and excitations) increases the chance of critical molecular and cellular consequences even though the number of separate molecules which are damaged must be less than when the same total amount of atomic damage is sparsely scattered in space.

The vast majority of initial atomic and molecular damage is apparently of little or no relevance to the final cellular consequences of interest. Even the vast majority of DNA damage, as measured by initial direct ionizations ($\gtrsim 10^3$ cell^{-1} Gy^{-1}), ssb ($\sim 10^3$), dsb ($\sim 10^2$) or even unrejoined breaks after a substantial repair interval (~ 10 cell^{-1} Gy^{-1}) does not lead to cell inactivation ($\sim 0{\cdot}2$–1 lethal events cell^{-1} Gy^{-1}) (Goodhead *et al.* 1985). This raises the question as to whether, simply by chance, only a small proportion of these points of damage become lethal, whether some points of damage are qualitatively different (more severe) or whether the integrity of only a small proportion of the DNA is critical for cell survival. The nature and severity of the molecular damage is clearly an important factor, but current evidence also suggests that full integrity of only a small percentage of the DNA complement of a cell is critical. This is implied by the observation that only a minority ($\sim$1–5 per cent) of the decays of DNA-incorporated ^{125}I actually lead to cell inactivation, despite the fact that they almost all produce very large local, and apparently unrepairable, damage to the DNA at the site of decay (Charlton 1986). It is reinforced by the observation that narrow tracks of even extremely high-LET particles such as slow uranium ions of 20,000 keV μm^{-1} can have a large probability of passing through a cell nucleus without inactivating it (Kraft 1987), even though each track should directly intersect the DNA many times ($\gtrsim 10$), producing a very large concentration of local damage at each intersection (Goodhead *et al.* 1980).

Given the large variety and large numbers of types of DNA damage, most of which are apparently not relevant to the final cellular effect, it seems inevitable that many simple biochemical assays will be heavily dominated by damage which is of little relevance to the characterization or understanding of the effects of radiation on cells. It is a major challenge to develop and validate systems which do relate directly to that minority of initial physical and chemical damage which is of critical importance.

2. Historical comments

As early as the 1940s it was suggested that localized clusters of ionizations were predominantly responsible for critical damage to DNA structures in eukaryotes

(Lea 1947). The biophysical analyses of Howard-Flanders (1958) indicated that the spatial extent of the critical clusters extended over a few nanometres. These dimensions resulted from the analysis itself, without any assumptions as to the molecular nature of the target volumes or the relevance of DNA. Similar concepts were applied by Barendsen (1964), and later Goodhead *et al.* (1980), to various mammalian cells, and these led to the conclusion that critical damage was due to clustering of ionizations over dimensions of 2–10 nm. All these analyses were based on rather crude descriptions of radiation tracks as one-dimensional structures composed of a fairly simple distribution of ionizations and clusters, these being the best microscopic descriptions available at the time.

Other biophysical models were developed meanwhile, which put prime emphasis on energy deposition over very much larger distances (up to a few thousands of nanometres). In contrast there was also a gradual accumulation of more direct experimental evidence reinforcing the critical importance of very local concentrations over distances of 1–50 nm. These included experiments with ultrasoft X-rays and heavy ions, both of which showed the importance of concentrations over small distances (see Goodhead 1982), as well as characterization of radiation-induced mutants as mostly large structural losses or alterations (Thacker 1986) and implication of radiation-induced DNA dsb in cellular effects, both of which suggest that the critical local damage is complex in nature. Almost all mechanistic biophysical models of radiation action now assume that the initial critical damage is highly localized and complex, at least for the lower dose range up to perhaps a few Gy (see summaries in Goodhead 1987a,b). Much longer-range multi-track effects must, of course, be involved when dose responses (including logarithm of survival) are observed to be nonlinear, but even for this component most current models assume that the points of primary damage are highly localized and complex, and are then followed by subsequent long-range interaction or repair modulation (Goodhead 1987a,b).

In recent years it has become possible to obtain greatly improved descriptions of the microscopic features of radiation tracks, down to nanometre dimensions. This is achieved by Monte Carlo computer simulations of radiation tracks which include each atomic interaction (ionization or excitation) of the primary charged particles and all their secondaries until they come to rest (Paretzke 1987). From these it is possible to analyse the three-dimensional structures, of statistically representative numbers of tracks, over dimensions down to less than 1 nm (Nikjoo *et al.* 1989). Such studies have further reinforced the apparent importance of highly localized clusters of atomic damage in producing the complex molecular damage of biological importance.

This emphasis on local concentrations of ionizations (and excitations) within or very near to the target molecule runs somewhat against a common approach used in radiation-chemistry studies where prime emphasis is put on diffusion of simple water–radiolysis products such as the hydroxyl radical in dilute solutions. However, some groups working from the radiation chemistry point of view have also been led by their experimental results to infer that the primary molecular damage of importance in mammalian cells is produced by a localized cluster of atomic interactions overlapping the DNA to produce a local multiply damaged site (Ward 1988). The relative unimportance of simple diffusing radicals is then probably due to their very small diffusion lengths in the intracellular environment, and to the cells' ability to repair very efficiently simple damage to the DNA but not the more complex damage. The very low probability of two diffusing hydroxyl radicals

reaching adjacent strands of DNA is illustrated by the model calculations of Ito (1987), in which <2 per cent of the dsb arise from two hydroxyl radicals, although single hydroxyl radicals are involved in ~50 per cent of dsb by acting in concert with a direct ionizing.

3. Track structure analysis and implications

Many descriptions have been used in attempts to identify the biologically relevant features of the 'quality' of radiation tracks (figure 3). Most of these describe only average properties over dimensions much too large in relation to targets of DNA dimensions.

We have in recent years been pursuing an extensive programme of scoring the absolute efficiencies with which different radiations can deposit concentrations of energy in small target volumes of dimensions from 1 nm upwards. In some respects this is similar to obtaining the 'proportional counter' quantities illustrated as (b) in figure 3, but with the important differences that the volumes under present study are much too small to allow direct experimental measurement by the usual proportional counter methods and that the results are expressed simply in terms of energy deposition, without division by length or mass, so that they may be more readily related to likely molecular consequences.

Such track structure analyses and comparison with observed biological effectiveness of the radiations can suggest critical classes of initial damage and thereby guide future studies of DNA damage and repair of main relevance in mammalian cells. Some suggestions are given below.

Figure 4 shows some of the results which have been obtained for a target cylinder of 2 nm diameter and length, randomly positioned in a water medium uniformly irradiated.

Notable features in figure 4 include:

1. The frequency of a hit of any size in a given single target is extremely small ($\sim 10^{-6}\,Gy^{-1}$). Hence the probability of two separate hits occurring by overlap of separate tracks is negligibly small except at extremely high doses ($\gtrsim 10^{5}$ Gy), so only single-track effects need be considered for these targets.
2. The total numbers of DNA segments hit per cell are quite large ($\sim 10^{3}\,Gy^{-1}$) and are heavily dominated by small hits, each corresponding to only a few ionizations or excitations. The numbers are of similar order of magnitude to the numbers of DNA ssb. However, the biological effectiveness of the radiations relative to one another are totally inverse to the observed effectiveness for most cellular effects. From this it may be inferred that sparse ionizations or excitations are not of great relevance to biological effect.
3. For somewhat larger energy depositions of, say, $E \gtrsim 100$ eV (corresponding to $\gtrsim 10$ ionizations and excitations) the radiations follow the same sequence of effectiveness as does their ability to produce DNA dsb and to produce cellular effects such as inactivation, chromosome aberrations and mutations. The absolute numbers of such hits per cell are still quite substantial (~ 20–$10^{2}\,Gy^{-1}$) and correspond fairly closely to the absolute numbers of initial dsb which are measured experimentally (Charlton *et al.* 1989, Goodhead and Nikjoo 1989).
4. Considerably larger energy depositions are produced efficiently only by the high-LET radiations.

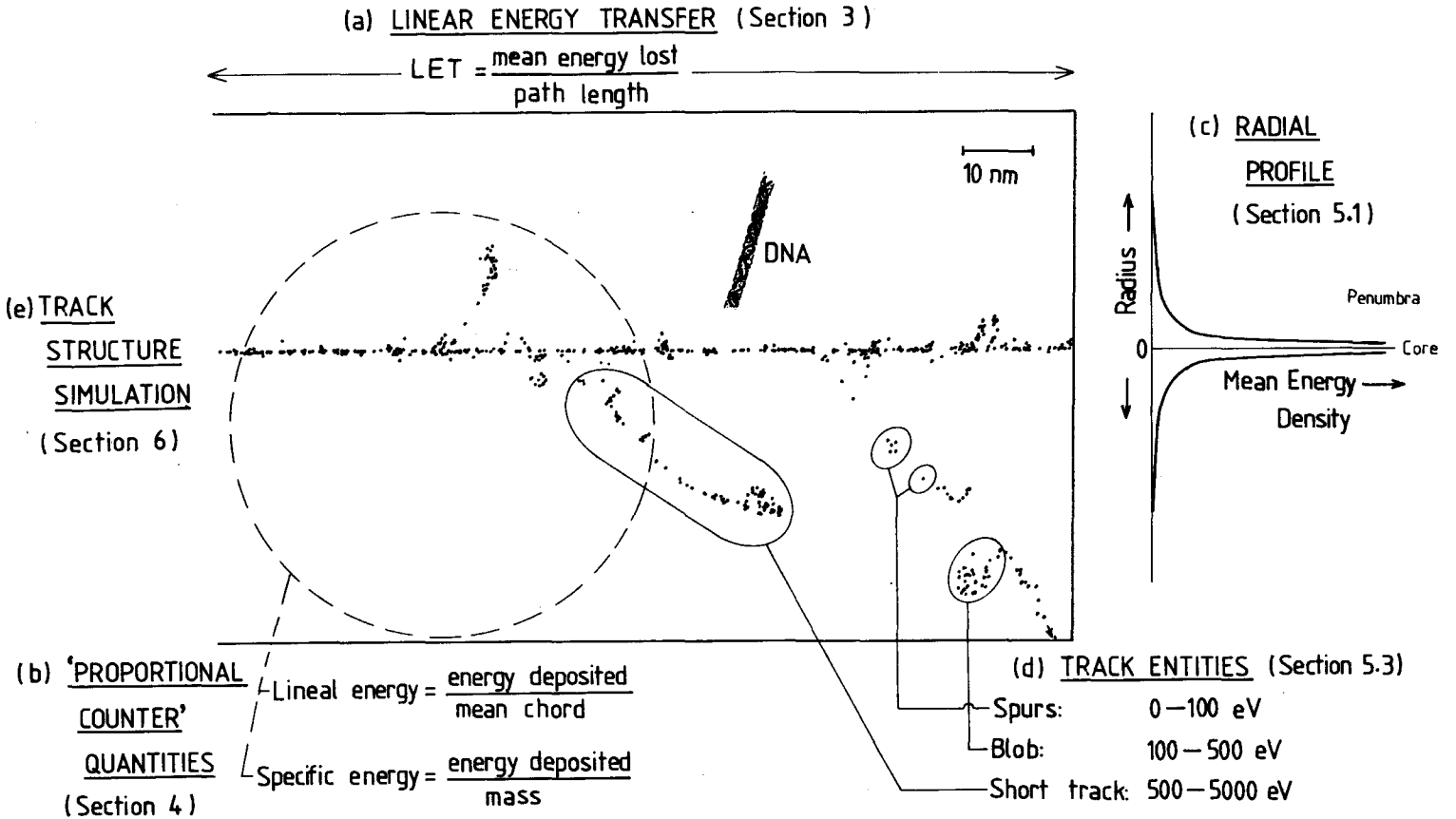

Figure 3. Illustration of a short segment of a Monte Carlo simulated track of an 8 MeV α-particle, showing some of the microdosimetric descriptions which have been used. (Reproduced, with permission, from Goodhead 1987c.) The Sections referred to in the Fig. are text in Goodhead (1987c).

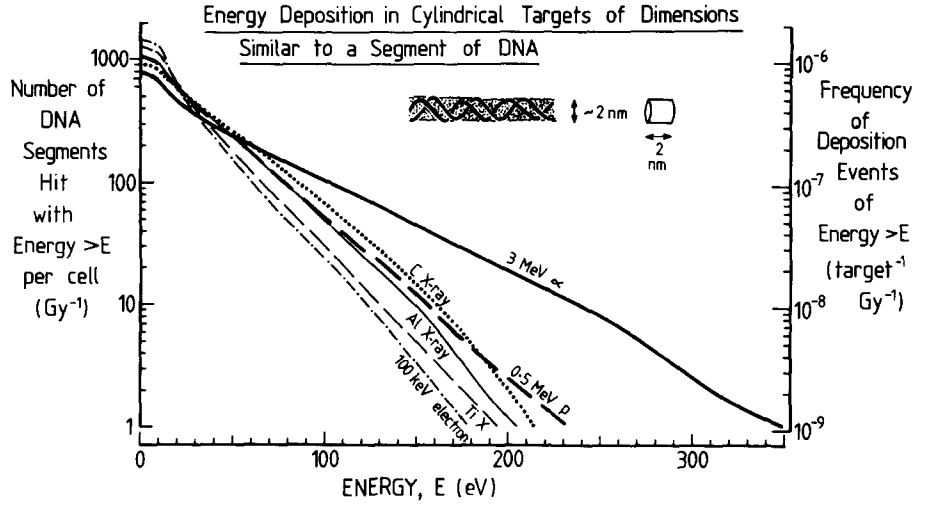

Figure 4. Absolute frequencies of energy deposition in a small (2 nm × 2 nm) cylindrical target randomly positioned in water irradiated with various radiations. If these targets are identified as DNA then the left-hand axis shows the number of such depositions in a single cell. Corresponding average numbers of ionizations plus excitations in the target can be estimated by dividing the energy E by approximately 10 eV. The curve for 100 keV electrons is representative of most low-LET radiations and the curves for ultrasoft X-rays (Ti, Al and C) represent exclusively electron track-ends (Goodhead and Nikjoo 1989). (Reproduced from Goodhead & Nikjoo 1989.)

5. Although high-LET radiations are the most effective at producing large energy depositions they do nevertheless produce large numbers of smaller depositions, and therefore should be well able to produce all the classes of molecular damage produced by the low-LET radiations.

Comparison between the radiations can be facilitated by expressing curves such as in figure 4 relative to a reference radiation as in figure 5 (in which 100 keV electrons are chosen as low-LET reference). This shows, as noted above, that the relative biological effectiveness (RBE) for production of sparse damage (small energy depositions) is small ($\lesssim 1$) for all the radiations (unlike cellular RBEs); that the RBEs for production of clustered damage rise to quite realistic values in the region of $\gtrsim 100$ eV; and that the RBEs for α-particles become extremely large for energy deposition > 200 eV in the DNA-sized targets.

Initial damage in material in the very near vicinity of the DNA, such as protein and bound water, may also be of considerable relevance in determining the quantity and type of damage to DNA and its repairability. Some assessment of this can be obtained by considering the energy deposition frequencies in cylinders somewhat larger than that illustrated in figure 4, say with dimensions of 5 or 10 nm. These frequency distributions show features which are broadly similar to those discussed above for the 2 nm cylinders, although the numerical values are, of course, different (Goodhead and Nikjoo 1989).

Given the number and variety of substantial initial energy depositions in, or near to, DNA it seems important to establish what complex radiation chemistry might follow, what types and complexity of molecular changes might occur, and

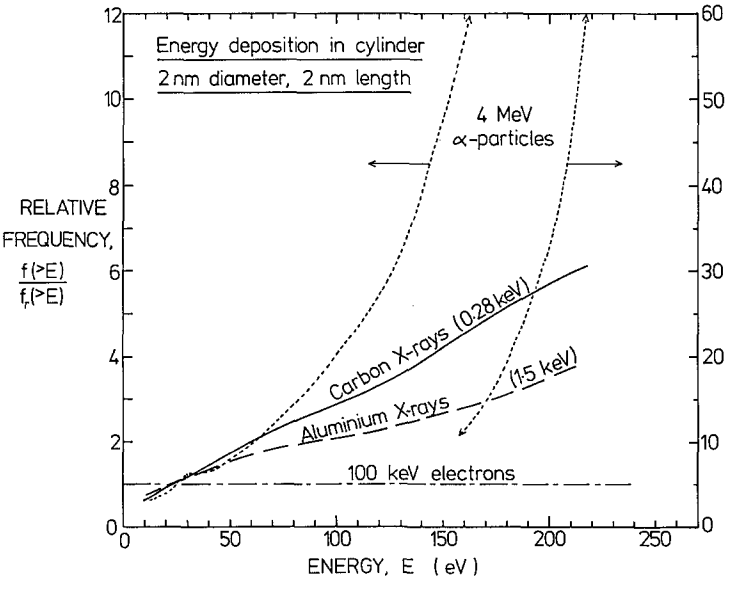

Figure 5. Relative frequencies of energy deposition in a small (2 nm × 2 nm) cylindrical target randomly positioned in water irradiated with various radiations, relative to 100 keV electrons as reference radiation. (The accuracy of relative frequencies for the larger energy depositions is severely limited by the scoring statistics of these very rare events in the reference radiation. The 100 keV electron distribution as used here is based on a total of $2{\cdot}3 \times 10^4$ hits, but only 6 of these are for $E > 200$ eV.)

how these can or cannot be repaired by the cells. It seems reasonable to expect that the answers to these questions will vary considerably across the spectrum of damage. Most single biochemical assay systems will reveal only a very narrow portion of the true variety and complexity of possible damage.

From comparisons of the track structure analyses with experimental data on biological effectiveness of diverse radiations, I suggest that the continuous spectrum of initial physical damage from ionizing radiations be considered in four broad classes (table 1), each with its own implications in terms of the nature of the radiation chemistry, biochemical damage and repair which follow and its relevance to cellular effects. These classes may serve to guide development of assays to study various components of the spectrum of damage and to assess their biological importance.

1. *Sparse ionizations/excitations.* This damage would dominate most simple radiation-chemistry and biochemical assays but is probably of little biological relevance in mammalian cells. The frequency of occurrence is inverse to observed cellular RBEs. This damage may be closely related to ssb.
2. *Moderate clusters.* The frequency of occurrence approximately follows cellular RBEs for low-LET-like effects. This damage has the general radiobiological features characteristic of low-LET radiations, with its probability of cellular consequences being readily modifiable. Such clusters may be a prime cause of DNA dsb, of either a simple or somewhat complex nature. These clusters occur particularly in electron track-ends. Different cell types may respond more or less to the lower-energy end of this class, depending on

Table 1.

Class	Initial physical damage	Typical energy and target dimensions	Possible target	Frequency of occurrence (cell^{-1} Gy^{-1})†	Comment
1	Sparse	Few tens of eV within ~2 nm	DNA segment	~10^3	Little biological relevance?
2	Moderate cluster	~100 eV within ~2 nm	DNA segment	~20–100	Characteristic of low-LET; ~repairable
3	Large cluster	~400 eV within 5–10 nm	Nucleosome	~4–100	Characteristic of high-LET; ~unrepairable
4	Very large cluster	~800 eV within 5–10 nm	(Nucleosome)	~0–4	Unique to high-LET; unrepairable; relevance?

†These frequencies assume that the targets are as in the previous column and that all the cell's DNA (~6 pg) is arranged in this way (Goodhead and Nikjoo 1989).

their repair capabilities; in this case cells which show a 'shouldered' dose–response may respond least to the lower end.

3. *Large clusters.* The frequency of occurrence approximately follows cellular RBEs for high-LET-like effects (Goodhead *et al.* 1985). Slow α-particles of a few MeV are the most effective. This damage has the general radiobiological features characteristic of high-LET radiations, including being essentially unmodifiable. It may include complex damage to DNA in association with adjacent molecules and structures.
4. *Very large clusters.* These are unique to high-LET radiations, especially α-particles and heavier ions, and are totally unattainable by low-LET radiations. Thus unique biochemical and cellular consequences could follow, in principle, yielding infinite RBEs. The practical biological relevance of this relatively rare damage is not known, but there is a least one known system, involving sister chromatid exchanges, which does apparently show such a unique high-LET effect (Aghamohammadi *et al.* 1988).

4. Conclusion

Biophysical analyses of radiation tracks emphasize the importance of very local clustering of atomic damage within a track over microscopic distances as small as a few nanometres. They show that there must be a wide spectrum of initial physical damage within or very near to relevant macromolecules, such as DNA, and that the chemical, biochemical, repair and cellular consequences should differ considerably across this spectrum. An attempt has been made to divide this spectrum into four broad classes in order to guide development and application of assays which may better reveal the complexities and relevance of damage to DNA, and associated structures, within these classes.

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