Elementary Concepts of Radiobiology

Dosimetry
As(201,463),(828,838) noted in Appendix E, biological effects are caused by the disruption of chemical bonds when radiation is incident on tissue. To a first approximation, this is proportional to the energy absorbed per unit volume. The absorbed dose, usually referred to simply (but inappropriately) as dose, is the average energy deposited per unit mass inside a small volume. The volume must be small enough for the average energy to be constant. It must also be large enough to contain many molecules or cells so that statistical fluctuations in energy deposition are not significant. The dose rate is the rate at which this energy is being deposited, or dose per unit time. For charged particles, it is equal to the dose per particle, times the number of particles traversing the target volume per unit time.

In most situations of interest, the deposited energy is closely related to the energy lost by the incident particles. However, this may not always be the case. For example, high-energy electrons are produced by charged particles traversing a cell. These high-energy electrons may escape, depositing their energy in other locations, outside the cell. At low dose rates, only one or a few particles are likely to traverse a cell, and the energy deposited in the cell is less than the energy lost by the particles. However, when a large number of particles is present, then electrons generated outside the cell may compensate for those that are lost. Thus, the concept of absorbed dose incorporates many assumptions and approximations that disciplines such as microdosimetry attempt to address. Nevertheless, the approximations are good enough that dose is used as the basis for estimating risk for x-rays and gamma rays. For historical reasons, x-rays have been used as the standard reference radiation with which all other types of radiation have been compared. The unit of absorbed dose is the Gray (Gy); it is equal to an average energy deposition of 1 Joule per kilogram (J/kg). An older unit, the rad, enjoys fairly frequent unofficial usage (one Gy is equal to 100 rad).

As was seen in Appendix E, heavy charged particles deposit energy at a very high density -- high LET -- which can be thousands of time higher than that deposited by x-rays and gamma rays (often referred to as low-LET radiation). The electrons released in tissue by x-rays have mean LET values of 2-3 keV/µm, while the gamma ray sources have mean LET values in the range of 0.2 to 0.5 keV/µm. While low-LET secondary electrons can pass through the spacing (~3 nm) between DNA strands without interacting, some high-LET ions can produce an ionization trail so large that it inactivates nearly every cell it traverses.

For heavy charged particles, however, different types of radiation do not produce the same observed effect at the same observed dose. This is to be expected, because the microscopic distribution of deposited energy and, hence, the chemical processes deriving from it, are not the same even though the average energy deposition (the
absorbed dose) may be the same. The differences in biological action for different types of radiation at the same absorbed dose are known as the “quality” of the radiation.

In the field of radiation protection, the dose equivalent, H, has been used to normalize biological damage to that of x-rays, by means of the relationship \( H = QD \), where \( Q \) is the quality factor defined as a function of LET. The unit of dose equivalent is the Sievert (Sv), where 1 Sv is presumed, for the purposes of radiation protection, to have the same biological consequences as 1 Gy of x-rays.

**Cells and Tissues**

The basic unit of the living organism is the cell. The interior of cells is highly organized. Mammalian cells, as opposed to bacterial cells, have a central core, the nucleus, separated from the rest of the cell by a semipermeable membrane. The cell itself is contained in a similar membrane, which is usually negatively charged on the outside and positively charged on the inside. Surface charges are sustained by layers of lipid molecules (soluble fats) in the membrane. Charged and neutral atoms and molecules can be transferred by passive transport through pores or active transport through the folds of proteins embedded in the membrane.

Within the cell, the deoxyribonucleic acid (DNA) molecules contain the information required for the synthesis of intracellular proteins, for cell reproduction and for organization of the tissues and organs. Other cellular structures participate in cellular function, but DNA is by far the component most sensitive to radiation and, hence, the action of radiation on living cells is most often considered on the basis of the interaction of radiation with DNA.

Cells divide under the control of chemical signals provided by their environment, including molecules generated by other cells. During development of an organism, the dividing cells differentiate into tissues and organs. Some adult tissues maintain “pluripotent stem cells” which, when stimulated to divide, can replenish depleted tissues, such as blood or the intestinal lining. Cell division takes place in a well-defined cell cycle, consisting of a resting stage, a stage where DNA is synthesized to provide double the original amount, a further resting stage, and a stage where actual division of the cell into two daughter cells takes place. In the adult organism most cells are shunted aside into a longer resting stage that does not involve continued proliferation.

Cell death in biological systems can be separated into two distinct forms: necrotic death and programmed death or apoptosis. Cell death is defined generally as loss of reproductive ability, since seriously damaged cells are often able to continue to function, as long as the chemical sites involved in this function are not themselves damaged by the radiation. Cell survival is an end-point best measured in the laboratory, as the ability of cells to divide into colonies; in living organisms, cell death only becomes manifest when the function of an organ or tissue is impaired.
The cell cycle is monitored by a multitude of chemical control systems. A major component of cellular defense against DNA damage consists of cell cycle checkpoints, that is, monitoring systems for DNA damage that temporarily halt transcription (the synthesis of RNA leading to protein synthesis) and/or replication (the synthesis of DNA) until the damage (referred to in general terms as “lesions”) are repaired. When defects in DNA cannot be repaired, or are too extensive, the cell cycle control system can induce apoptosis in the cell and eliminate it.

The expression of damage in tissue is complicated by the presence of up to 50 cell types per tissue, and by the interactions among them. Homeostasis (the requirement to keep the properties of the internal environment of the organism within operating limits) is maintained through a web of soluble growth factors and hormones, insoluble extracellular matrix components, and cell surface receptors that communicate these signals to individual cells as well as between cells. Research questions need to be addressed, wherever possible, at the tissue level rather than in cell culture, so that the influence of the microenvironment can be assessed.

**Radiation Effects**

The diameter of a mammalian cell is typically of the order of $\frac{1}{1000}$ in. The nucleus can take up anywhere between 10% and 90% of the cell’s volume. Inside the nucleus, the DNA is tightly wound into a tiny double helix, 100 times smaller than the cell. Thus, passage of sparsely ionizing radiation, such as x-rays, is not likely to result in frequent, direct ionization of even one bond on a DNA molecule. Radiation effects on the DNA are more likely to occur because molecules in the surrounding material, principally the surrounding water, have become ionized and, hence, chemically very reactive. When such molecules diffuse close enough to the DNA, they may undergo chemical reactions that can significantly alter the information stored in the DNA or its function. However, the densely ionizing central region of a charged particle traversing the cell has dimensions comparable to that of the DNA molecule. The passage of such a particle can cause one or more ionizations in every single DNA molecule it traverses. When the incident radiation deposits energy directly in the target DNA molecules, the process is referred to as a “direct” effect.

Of all the mechanisms resulting in initial damage to DNA, strand breaks are the most important. Breaks in a single strand are repaired efficiently by intracellular repair mechanisms. Double-strand breaks can occur as two neighboring single-strand breaks caused by direct action or as the result of the interaction of two independent single-strand breaks, separated by less than a critical distance. The magnitude of that distance is not known at present. Double-strand breaks are repaired much less efficiently than single-strand breaks and are much more likely to lead to cell death.
Modification of cell function can result from non-lethal changes in DNA leading to either benign or malignant cell proliferation ("neoplastic transformation"). This is an initial event in a sequence leading to cancer. A schematic depiction of the possible pathways leading from this event to uncontrolled proliferation and, possibly, cancer, is shown in Figure F.1. Further events, resulting from subsequent radiation or stimulation by so-called promoting substances, need to take place before the cell can be considered "precancerous". Precancerous cells may not always lead to cancer; further changes in the cell and surrounding tissues are required for this so-called "progression" stage. Even in the absence of cancer initiation, permanent changes in cellular DNA may occur as mutations. Such mutations, when they occur in reproductive cells may become inheritable and manifest in the progeny of the irradiated organism. These changes, in a cell that has maintained reproductive integrity, are known as "genetic effects".

The effects of radiation action are measured, according to the different endpoints, in terms of number of colonies formed by surviving cells, number of cells manifesting a measured change, probability of tumor formation, etc. The effects are also time-dependent, as shown in Figure F.2. Proliferative tissues, where cells divide relatively rapidly (e.g., the intestinal lining, blood cells), will show a fairly large initial damage due to cell killing but will also recover rapidly if cells are available to replenish the tissue loss. Non-proliferating or slowly-proliferating tissues will show damage slowly, as cells die off, but will not show recovery because there are no dividing cells to replenish the tissue. Late effects, due to accumulated genetic damage in surviving cells, can occur in both cases.
From the point of view of radiation protection, effects fall into two categories. When the effects are certain to be seen in the irradiated individual the effects are called “deterministic”. Relatively large doses of radiation are required to cause such effects, because the organism has the means to compensate for tissue damage. However, once an individual threshold is exceeded, the severity of the effect increases with increasing radiation dose. Examples of acute or early deterministic effects are skin reddening or radiation burns, and nausea or vomiting caused by destruction of cells in the intestinal lining. Examples of chronic or late deterministic effects are lens opacification (cataracts), organ atrophy, and a decrease in germ cells leading to sterility. The threshold where the destruction of non-proliferating brain cells leads to measurable changes in behavior is not known.

When the effects of radiation exposure on the exposed individual cannot be predicted, so that there is a probability, but no certainty of a given effect, the effect is called “stochastic”. Stochastic effects arise at the cellular or subcellular level and lead to an all or none response, such as the induction of cancer or of mutations leading to genetic effects. The probability of the effect increases with absorbed dose, but the severity of the effect (e.g., death) is not related to dose. The induction of stochastic effects is considered to be the principal consequence of low doses of ionizing radiation, and in general is delayed relative to the time of exposure. These distinctions reflect differences between cellular effects and tissue effects as illustrated in Figure F.3 - F.4.

Figure F.3 is a model calculation of cell survival. The model is based on experimental measurements of survival of cells in culture. Figure F.4 is a similar calculation for “transformation”, i.e., loss of some characteristic, such as contact inhibition, thought to be indicative of an initial, possibly pre-cancerous state. Survival of cells irradiated by x-rays has a broad shoulder, which is generally attributed to the capacity of cells to repair radiation damage. In this case, the cells whose response is modelled were allowed to grow in culture before being fixed for study. Densely ionizing particles, like iron nuclei, cause so many lesions in the DNA of a cell that no repair can be seen to occur. Intermediate ionization, such as that due to carbon ions, does not result in significant repair, but is also less efficient at killing cells.
Surprisingly, not all cells traversed by charged particles, even ones as heavy as iron nuclei, are killed. Some of the cells are transformed. In culture, pre-cancerous transformation increases in direct proportion to dose. As would be expected, high-LET iron is much more effective than high-LET C nuclei or low-LET x-rays. There is only set of heavy-ion data available for actual tumor induction in tissue. These data were obtained for tumor prevalence (the probability of observing a tumor at a given time after irradiation) in the Harderian gland of mice, and are plotted in Figure F. 5. A high tumor prevalence can be seen at relatively low doses of iron. Furthermore, the response is not proportional to the dose but increases in a non-linear way. The decrease in tumor prevalence beyond the maximum is probably due to the fact that too many cells are damaged, or damaged beyond the capabilities of the organism repair system, and simply do not survive.

From considerations such as the above, it is clear that different types of radiation do not result in the same type of effect. In Figure F. 4, inducing a level of 0.001 transformed cells per surviving cell requires 4 Gy of x-rays, but only 1 Gy of Fe: the Fe is 4 times as effective as x-rays; in Figure F. 5, a 30% prevalence of Harderian tumors is the result of approximately 3 Gy of gamma rays, but of only 1 Gy of Fe: in this case, the Fe is approximately 3 times as effective as gamma rays. This ratio of doses to produce the same effect describes the relative biological effectiveness, or RBE, of different types of radiation; to a first approximation it is a function of LET. It is used to describe the “quality” of the radiation.
Figure F. 6 illustrates the dependence of RBE on LET for transformation of a mouse cell; for other cell systems in culture, the RBE has a similar shape. It increases with LET up to a peak around 100 keV/µm, and then decreases rapidly. This behavior has also been found for tissues in culture. For Harderian gland tumor prevalence, however, the RBE has been found to remain at a value of approximately 30 for particles between Fe and Niobium.

This behavior, in the case of cells in culture, is attributed to the fact that the probability of inducing the observed effects increases with LET, for high-LET particles, but that the efficiency of x-rays to produce similar effects, especially at low doses, is considerably diminished. Thus, the ratio of x-ray dose to particle dose that defines LET, decreases reflecting the x-ray inefficiency. From a different perspective, the high ionization density at the core of a particle path means that, at a microscopic level, HZE particles do not deposit energy at a low dose; they only deposit very high doses in very small volumes, so that the average appears to be lower than the biological effectiveness would warrant.

A further indication of the dependence of radiation effect on tissue is shown in Table I, where the relative contribution of individual tissues to the probability of fatal cancer has been listed. It is clear that some tissues are more sensitive than others to initial damage, have different mechanisms for repair, repopulation, and replacement of damaged cells, and offer different access for treatment.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Respiratory System</td>
<td>1.90</td>
<td>1.50</td>
</tr>
<tr>
<td>Digestive System</td>
<td>1.70</td>
<td>2.90</td>
</tr>
<tr>
<td>Other solid tumors</td>
<td>3.00</td>
<td>2.20</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1.10</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>7.70</td>
<td>8.10</td>
</tr>
</tbody>
</table>

Table I. Relative contribution of individual tissues and organs to the probability of fatal cancer.

BEIR V data, summarized in: E. Hall, Radiobiology for the Radiologist (cf. Bibliography)
accordingly, for devising accurate radiation limits.
Elementary Concepts of Shielding

Radiation Transport
Shielding is the use of materials to mitigate the effects of incident radiation, by reducing the intensity of the radiation inside the shielded volume, by changing the deleterious properties ("quality") of the radiation, or both.

Examples of reducing the intensity of radiation are: attenuation of x-rays by absorption of photons in a lead curtain; attenuation of neutrons by nuclear interactions in hydrogenous materials; stopping of high-energy heavy ions in lunar regolith.

Examples of changing radiation quality are: moderation of neutrons in hydrogenous materials, which changes their energy but not their number; projectile fragmentation in spacecraft shielding, which results in lighter pieces of the incident projectile with less ionization density (LET).

Most shielding materials will change the energy, direction and kind of particles comprising the radiation field. The iron Bragg curves of Fig. E.2 show how the relative dose decreases in a water absorber. This decrease is due to a combination of effects. On the one hand, incident Fe nuclei suffer nuclear interactions. In some of these nuclear interaction, parts of the Fe nuclei are emitted approximately in the same direction and with the same velocity as the incident nucleus. These parts are lighter nuclei with lower charge $Z$ (fewer protons) and they ionize less, proportional to $Z^2$. In other reactions, nuclei of Fe may fragment entirely and be removed from the stream of particles. On the other hand, the Fe nuclei and the nuclear interaction products that do not interact continue losing energy. The slower particles have greater LET, resulting in higher relative doses. Finally, near the end of their range, the particles stop, and are removed from the radiation field; the heaviest particles with the highest charge lose most energy and are stopped first.

Shielding materials are generally “thick” materials, in the sense that they present enough matter to the incident material so that the energy losses of incident charged particles can be large (to the point of stopping in the material) or multiple nuclear interactions can occur to successive generations of secondary particles. The calculation of the number of particles, and of their kinds, energies and directions inside or behind any material is known as a "radiation transport" calculation. It is the means to predict how the radiation environment external to any human habitat is transformed by the presence of the materials of which the habitat is constructed.

Radiation transport calculations require accurate accounting, at each generation of interactions, of each particle’s change of identity, energy, and direction. In the case of neutrons, where the number of particles is small, and the different kinds of particles are limited, Monte Carlo methods have been used to make such calculations. In a Monte Carlo calculation, random numbers are generated for the particle position, energy and direction and the probability of a nuclear interaction is computed, yielding a set of numbers describing the particle’s new energy, position, and direction. This particle is followed until it is removed from the radiation field, and a similar computation is started for the next particle. If very large numbers of particles need to be simulated, Monte Carlo calculations can take a very long time and be very costly.
For modeling the transport of nucleons (neutrons and protons) through arbitrary target materials, a deterministic nucleon (BaRYoN) TRaNsport code, named BRYNTRN, has been developed by NASA at the Langley Research Center. The current version of the code accepts continuous spectral distributions from SPE / GCR protons as input. For modeling the transport of GCR (nucleons and HZE particles) and their reaction products through arbitrary target materials, NASA uses a deterministic HZE TRaNsport code, named HZETRN. Computer codes for the propagation of GCR also exist in Russia and Europe.

**Shield Material Characteristics**

Desirable shielding materials will result in high energy loss (stopping power) by the incident particle, while at the same time resulting in a low probability of nuclear interactions that might lead to projectile fragments. Since energy loss depends on the number of electrons, while nuclear interactions depend on the number of nucleons, the best shielding materials are likely to be those that have the highest ratio of electrons to protons. Hydrogen, with exactly one electron and a one-proton nucleus, has an electron/proton ratio of 1, higher than that for any other element, and is thus the most desirable component to use in shielding materials. Wilson and his colleagues at LaRC have done extensive analyses of hydrogen-containing materials. A discussion of their structural and other properties, and of the issues involved in shielding optimization can be found in the workshop report “Shielding Strategies for Human Space Exploration.”

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**Figure G. 1. Primaries and Secondaries Inside 5 g/cm² of Aluminum**
The results of a conventional radiation transport calculation specify the physical characteristics of the radiation field inside or behind shielding. However, in order to estimate risk, it is necessary to calculate the dose, dose equivalent, or other properties of the radiation field. As illustrated in Fig. G.1, the contribution of the various particle species inside 5 g/cm$^2$ of Al shielding is different for different biological endpoints, illustrating the requirement to characterize shielding efficacy in biological terms. As shown by Wilson and his colleagues, the biological characterization of shielding accentuates features not clearly distinguishable by use of conventional dose equivalent. Biological figures of merit are required for shielding optimization.