Radiobiology: Concepts and Basic Principles

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Michael G. Stabin

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9.1 Introduction

Very soon after the discovery of radiation and radioactivity short- and long-term negative effects of radiation on human tissue were observed. Adverse effects of X-rays were observed by Thomas Edison, William J. Morton, and Nikola Tesla; they independently reported eye irritations from experimentation with X-rays and fluorescent substances. These effects were thought to be eye strain, or possibly due to exposure to ultraviolet radiation. Elihu Thomson (an American physicist) deliberately exposed the little finger of his left hand to X-rays for several days, for a short time each day, and observed pain, swelling, stiffness, erythema, and blistering in the finger, which was clearly and immediately related to the radiation exposure. William Herbert Rollins (a Boston dentist) demonstrated that X-rays could kill guinea pigs and result in the death of offspring when guinea pigs were irradiated while pregnant. Henri Becquerel received a skin burn from a radium source given to him by the Curies that he carried in a vest pocket at times. He once was reported to have said: "I love this radium but I have a grudge against it!" The first death in an X-ray pioneer attributed to cumulative overexposure was to C.M. Dally in 1904. Radiologists and other physicians who used X-rays in their practices before health physics practices were common had a significantly higher rate of leukemia than their colleagues. A particularly tragic episode in the history of the use of radiation and in the history of industrialism was the acute and chronic biological damage suffered by the Radium Dial Painters [1]. Radium was used in luminous paints in the early 1900s. In factories where luminous dial watches were made, workers (mainly women) would sharpen the tips of their paint brushes with their lips, and thus ingested large amounts of radium. They had increased amounts of bone cancer (carcinomas in the paranasal sinuses or the mastoid structures, which are very rare, and were thus clearly associated with their exposures, as well as cancers in other sites) and even spontaneous fractures in their jaws and spines from cumulative radiation injury. Others died of anemia and other causes.

9.2 Stochastic Versus Nonstochastic Effects

There are two broad categories of radiation-related effects in humans, *stochastic* and *nonstochastic*.

M.G. Stabin
Department of Radiology and Radiological Sciences, Vanderbilt University, 1161 21st Avenue South, Nashville, TN 37232–2675, USA
e-mail: michael.g.stabin@vanderbilt.edu

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There are three important characteristics that distinguish them.

9.2.1 Nonstochastic Effects

Nonstochastic effects (now officially called "deterministic effects," previously also called "acute effects") are effects that are generally observed soon after exposure to radiation. As they are "nonstochastic" in nature, they will always be observed (if the dose threshold is exceeded), and there is generally no doubt that they were caused by the radiation exposure. The major identifying characteristics of nonstochastic effects are:

1. There is a *threshold* of dose below which the effects will not be observed.
2. Above this threshold, the *magnitude* of the effect increases with dose.
3. The effect is *clearly associated* with the radiation exposure.

Examples include:

- Erythema (reddening of the skin)
- Epilation (loss of hair)
- Depression of bone marrow cell division (observed in counts of formed elements in peripheral blood)
- Nausea, vomiting, diarrhea (NVD) – often observed in victims after an acute exposure to radiation
- Central nervous system (CNS) damage
- Damage to the unborn child (physical deformities), microcephaly (small head size at birth), mental retardation

When discussing nonstochastic effects, it is important to note that some organs are more radiosensitive than others. The so-called law of Bergonie and Tribondeau [2] states that cells tend to be radiosensitive if they have three properties:

- Cells have a high division rate.
- Cells have a long dividing future.
- Cells are of an unspecialized type.

A concise way of stating the law might be to say that "the radiosensitivity of a cell type is proportional to its rate of division and inversely proportional to its degree of specialization." So, rapidly dividing and unspecialized cells, as a rule, are the most radiosensitive. Two important examples are cells in the red marrow and in the developing embryo/fetus. In the case of marrow, a number of *progenitor* cells which, through many generations of cell division, produce a variety of different functional cells that are very specialized (e.g., red blood cells, lymphocytes, leukocytes, platelets). Some of these functional cells do not divide at all, and are thus themselves quite radioresistant. However, if the marrow receives a high dose of radiation, damage to these progenitor cells is very important to the health of the organism. As we will see shortly, if these cells are affected, in a short period this will be manifested in a measurable decrease in the number of formed elements in the peripheral blood. If the damage is severe enough, the person may not survive. If not, the progenitor cells will eventually repopulate and begin to replenish the numbers of the formed elements, and subsequent blood samples will show this recovery process.

In the fetus, organs and systems develop at different rates. At the moment of conception, of course, we have one completely undifferentiated cell that becomes two cells after one division, then four then eight, and so on. As the rapid cell division proceeds, groups of cells "receive their assignments" and differentiate to form organs and organ systems, still with a very rapid rate of cell division. At some point, individual organs become well defined and formed, and cell division slows as the fetus simply adds mass. But while differentiation and early rapid cell division is occurring, these cells are quite radiosensitive, and a high dose to the fetus may cause fetal death, or damage to individual fetal structures. This is discussed further below. On the other hand, in an adult, cells of the CNS (brain tissue, spinal cord, etc.) are very highly specialized and have very low, or no, rate of division. The CNS is thus particularly radioresistant. One important nonstochastic effect is death. This results from damage to the bone marrow (first), then to the gastrointestinal tract, then to the nervous system.

9.2.2 Stochastic Effects

Stochastic effects are effects that are, as the name implies, probabilistic. They may or may not occur in

any given exposed individual. These effects generally manifest many years, even decades, after the radiation exposure (and were once called "late effects"). Their major characteristics, in direct contrast with those for nonstochastic effects, are:

1. A *threshold* may not be observed.
2. The *probability* of the effect increases with dose.
3. You *cannot definitively associate* the effect with the radiation exposure.

   Examples include:

   - Cancer induction
   - Genetic effects (offspring of irradiated individuals)

9.3 Cellular Response and Survival

Much information on the biological effects of radiation has been obtained for many years through the use of direct experiments on cell cultures. It is of course far easier to control the experiment and the variables involved when the radiation source can be carefully modulated, the system under study can be simple and uniform, and the results can be evaluated over almost any period of time desired (days to weeks, or even over microseconds, such as in the study of free radical formation and reaction [3]). After exposure of a group of cells to radiation, the most common concept to study is that of cell survival. Typically, the natural logarithm of the surviving fraction of irradiated cells is plotted against the dose received.

As shown in Fig. 9.1, the simplest survival curve is a single exponential, and can be formulated as:

$$S = S_0 \, \mathrm{e}^{-D/D_0}$$

Here S is the surviving fraction, S_0 is the original number of cells irradiated, D is the dose received, and D_0 is the negative reciprocal of the slope of the curve, and is called the mean lethal dose. When cells receive dose D_0, the surviving fraction is 0.37, which is 1/e. This dose may also be referred to as the D_{37} dose, just as we define the LD_{50}, the lethal dose of radiation that will kill half of a population. Generally speaking, particles with a high linear energy transfer (LET) will show this form of a survival curve, while those

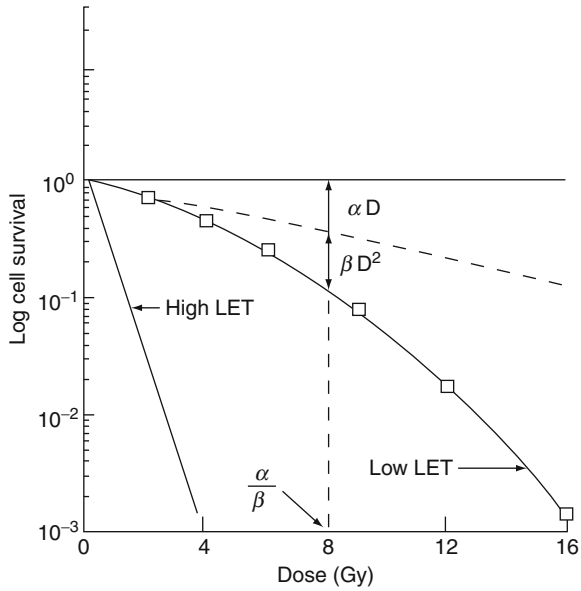

Fig. 9.1 Typical cell survival curve after exposure to low and high LET radiation. From Annals of the ICRP, Volume 37, Issues 2-4, Pages 1-332 , 2007 with permission

of low LET will have a more complicated curve, of the form:

$$S = S_0 \left[1 - \left(1 - \mathrm{e}^{-D/D_0}\right)^n\right]$$

Here n is the assumed number of targets that need to be hit in order to inactivate a cell. If $n = 1$, the equation reduces to the simpler form shown above. The usual curve, however, has a "shoulder," indicating that a certain amount of dose must be received before any significant effect on cell survival is seen. At higher doses, the curve attains the usual linear shape with slope $-1/D_0$. If the linear portion is extrapolated back to zero dose, it will intercept the y-axis at the "extrapolation number" n, which is numerically equal to the number of targets assumed to be relevant to the cells' survival.

Several factors affect the shape of the dose–response function other than the LET of the radiation, including:

- *Dose rate* – the LD_{50} of a population of cells will clearly increase as the dose rate at which a fixed dose D is delivered is decreased. Cells have a considerable capacity to repair radiation damage, and if time is allowed for repair, more radiation can be tolerated.

- *Dose fractionation* – if cells are given a cumulative dose D, but instead of being delivered all at once, it is delivered in N fractions of D/N each, the cell survival curve will show a *series of shoulders* linked together, because cellular repair is again ongoing between fractions. This is a strategy used in radiation therapy procedures to allow healthy tissues time for repair while still delivering an ultimately lethal dose to the tumor tissues.
- *Presence of oxygen* – dissolved oxygen in tissue causes the tissue to be sensitive to radiation. Hypoxic cells have been shown to be considerably more radioresistant. The effect of oxygen is sometimes expressed as the "oxygen enhancement ratio" (OER), which is the ratio of the slope of the straight portion of the cell survival curve with and without oxygen present.

Another expression of the standard model of cell survival gives the fraction of cells surviving the irradiation (SF) as a function of the dose delivered (D):

$$\ln(\mathrm{SF}) = -\alpha D - \beta D^2$$

where α and β are disease- or even patient-specific parameters related to radiosensitivity, and the ratio of these parameters determines the shape of the cell survival curve. A dose protraction factor, G, has been added to this model [4, 5] to accommodate the effect on cell kill by the change in absorbed dose rate:

$$G = \frac{2}{D^2}\int_0^{\infty}\dot{D}(t)\int_0^{t}\dot{D}(t')e^{-\mu(t-t')}\mathrm{d}t'\mathrm{d}t$$

where μ is the constant of sublethal damage repair and t' is a time point during the treatment prior to time t. The biologically effective dose (BED) [6, 7] has been defined as:

$$\mathrm{BED} = -\frac{\ln(\mathrm{SF})}{\alpha}$$

This quantity is defined for external beam radiotherapy and therapy with radiopharmaceuticals using the following equations:

For external beam radiotherapy:

$$\mathrm{BED}_{\mathrm{EBT}} = D_{\mathrm{EBT}}\left(1 + \frac{D_{\mathrm{EBT}}/n}{\alpha/\beta}\right)$$

and for radiopharmaceuticals (including the decay constant, λ, for the radionuclide and a term μ related to cellular response rate to radiation damage:

$$\mathrm{BED}_{\mathrm{TRT}} = D_{\mathrm{TRT}}\left(1 + \frac{D_{\mathrm{TRT}}\lambda}{(\mu+\lambda)(\alpha/\beta)}\right)$$

It has been shown that that these radiobiological arguments may be employed to combine radionuclide and external beam radiotherapy [8].

9.3.1 Mechanisms of Radiation Damage to Biological Systems

Radiation interactions with aqueous systems can be described as occurring in four principal stages:

1. Physical
2. Prechemical
3. Early chemical
4. Late chemical

In the *physical* stage of water radiolysis, a primary charged particle interacts through elastic and inelastic collisions. Inelastic collisions result in the ionization and excitation of water molecules, leaving behind ionized (H_2O^+) and excited (H_2O^*) molecules, and unbound subexcitation electrons (e^-_{sub}). A subexcitation electron is one whose energy is not high enough to produce further electronic transitions. By contrast, some electrons produced in the interaction of the primary charged particle with the water molecules may have sufficient energy themselves to produce additional electronic transitions. These electrons may produce secondary track structures (delta rays), beyond that produced by the primary particle. All charged particles can interact with electrons in the water both individually and collectively in the condensed, liquid phase. The initial passage of the particle, with the production of ionized and excited water molecules and subexcited electrons in the local track region (within a few hundred angstroms), occurs within about 10^{-15} s. From this time until about 10^{-12} s, in the *prechemical* phase, some initial reactions and rearrangements of these species occur. If a water molecule is ionized, this results in the creation of an ionized water molecule and a free electron. The free electron rapidly attracts other water molecules, as the slightly polar molecule has a positive and negative pole,

and the positive pole is attracted to the electron. A group of water molecules thus clusters around the electron, and it is known as a "hydrated electron" and is designated as e_{aq}^-. The water molecule dissociates immediately:

$$H_2O \rightarrow H_2O^+ + e_{aq}^- \rightarrow H^+ + OH\cdot + e_{aq}^-$$

In an excitation event, an electron in the molecule is raised to a higher energy level. This electron may simply return to its original state, or the molecule may break up into an H and an OH radical (a radical is a species that has an unpaired electron in one of its orbitals – the species is not necessarily charged, but is highly reactive).

$$H_2O \rightarrow H\cdot + OH\cdot$$

The free radical species and the hydrated electron undergo dozens of other reactions with each other and other molecules in the system. Reactions with other commonly encountered molecules in aqueous systems are shown in Table 9.1. Reactions with other molecules have been studied and modeled by various investigators as well [9–12].

The *early chemical* phase, extending from ~10^{-12} to ~10^{-6} s, is the time period within which the species can diffuse and react with each other and with other molecules in solution. By about 10^{-6} s most of the original track structure is lost, and any remaining reactive species are so widely separated that further reactions between individual species are unlikely [5]. From 10^{-6} s onward, referred to as the *late chemical* stage, calculation of further product yields can be made by using differential rate-equation systems which assume uniform distribution of the solutes and reactions governed by reaction-rate coefficients. Cells clearly have mechanisms for repairing DNA damage. If damage occurs to a single strand of DNA, it is particularly easy for the cells to repair this damage, as information from the complementary chain may be used to identify the base pairs needed to complete the damaged area. "Double strand breaks" are more difficult to repair, but cellular mechanisms do exist that can affect repair here also.

Table 9.1 Comparison of reaction rate coefficients and reaction radii for several reactions of importance to radiation biology[a]

Reaction	k (10^{10} M^{-1} s^{-1})	R (nm)
$H\cdot + OH\cdot \rightarrow H_2O$	2.0	0.43
$e_{aq}^- + OH \rightarrow OH^-$	3.0	0.72
$e_{aq}^- + H\cdot + H_2O \rightarrow H_2 + OH^-$	2.5	0.45
$e_{aq}^- + H_3O^+ \rightarrow H\cdot + H_2O$	2.2	0.39
$H\cdot + H\cdot \rightarrow H_2$	1.0	0.23
$OH\cdot + OH\cdot \rightarrow H_2O_2$	0.55	0.55
$2e_{aq}^- + 2H_2O \rightarrow H_2 + 2OH^-$	0.5	0.18
$H_3O^+ + OH^- \rightarrow 2H_2O$	14.3	1.58
$e_{aq}^- + H_2O_2 \rightarrow OH^- + OH\cdot$	1.2	0.57
$OH + OH^- \rightarrow H_2O + O^-$	1.2	0.36

[a] k is the reaction rate constant and R is the "reaction radius" for the specified reaction. The use of these concepts is explained in the physical chemistry literature

9.3.2 Bystander Effect

Other recent interesting experimental evidence has shown that energy deposition alone cannot always predict the occurrence of cellular changes, but that in some conditions, cells that have received no direct energy deposition from radiation may demonstrate a biological response, the so-called bystander effect. Brooks notes that "[t]he potential for bystander effects may impact risk from nonuniform distribution of dose or energy in tissues and raises some very interesting questions as to the validity of such calculations." Hall [13] notes that "[t]he plethora of data now available concerning the bystander effect fall into two quite separate categories, and it is not certain that the two groups of experiments are addressing the same phenomenon." Those two categories are:

1. *Medium transfer experiments* – a number of independent studies [13] have shown that irradiated cells may have secreted some molecule into the culture medium that was capable of killing cells when that medium was placed in contact with unirradiated cells. This bystander effect can be seen at radiation doses as low as 0.25 mGy, and does not appear to be significantly increased up to doses of 10 Gy. Medium transfer experiments have shown an increase in neoplastic transformation as well as genomic instability in cells that have not themselves been irradiated.

2. *Microbeam irradiation experiments* – accurately directed beams of radiation have facilitated the exposure of only specified cells in a culture medium to radiation, but effects in other, unirradiated, cells have been observed. Hall discusses a striking experiment, in which human fibroblasts were irradiated with microbeams of alpha particles, with cells of one population lightly stained with cyto-orange, a cytoplasmic vital dye, while cells of another population were lightly stained blue with a nuclear vital dye. The two cell populations were mixed and allowed to attach to the culture dish, and the computer controlling the accelerator was programmed to irradiate only blue-stained cells with ten alpha particles directed at the centroid of the nucleus. The cells were fixed and stained 48 h later, at which time micronuclei and chromosome bridges were visible in a proportion of the nonhit (i.e., orange-stained) cells.

Other studies have shown interesting effects, such as one involving irradiation of the lung base in rats, but in which an increase in the frequency of micronuclei was found in the shielded lung apex [10]. On the other hand, radiation of the lung apex did not result in an increase in the chromosome damage in the shielded lung base. This suggests that a factor was transferred from the exposed portion of the lung to the shielded part and that this transfer has direction from the base to the apex of the lung. In another experiment, exposure of the left lung resulted in a marked increase in micronuclei in the unexposed right lung. Experiments suggest that bystander effects are limited to the organ irradiated, and have been demonstrated primarily in experiments with alpha particles. These results challenge the traditional notion of the relationship of dose and effects.

9.4 Relevance of Radiation Biology to Radionuclide Therapy

9.4.1 Thyroid Disease

Clinical applications of dosimetry in radionuclide therapy vary in their application. Standardized methodologies have not been agreed upon, and results of different investigators may be difficult to compare. The advent of multimodality imaging (single photon emission computed tomography (SPECT)/CT or positron emission tomography (PET)/CT) and the incorporation of patient-specific 3D image in the dosimetric calculations along with radiobiolgical modeling will lead to a better characterization of radiation dosimetry during therapy applications. There is clear evidence that dosimetry can prove to be of practical benefit in clinical practice, but many physicians remain skeptical of the need for dosimetry in routine practice, although it is required in the clinical trial phase of new drug approval.

Maxon et al. [14, 15] used a dosimetric approach in the treatment of thyroid disease and concluded that a reliable response of the diseased tissue is not likely unless the radiation reaches or exceeds 85 Gy. Kobe et al. [16] evaluated the success of the treatment of Graves' disease in 571 subjects, with the goal of delivering 250 Gy to the thyroid, with the end-point measure being the elimination of hyperthyroidism, evaluated 12 months after the treatment. Relief from hyperthyroidism was achieved in 96% of patients who received more than 200 Gy, even for those with thyroid volumes > 40 ml. Individually tailored patient thyroid dosimetry was made to the targeted total dose, with ultrasound measurement of subject thyroid mass and adjustment of the procedure to account for differences between observed effective retention half-times between studies involving the tracer activity and the therapy administration. Two groups asserted that an absorbed therapeutic dose can be predicted by a prior tracer administration with a reasonable degree of accuracy that would enable patient-specific treatment planning [17, 18], and it has further been shown that the rate of hypothyroidism resulting from the treatment of Graves' disease with radioiodine is correlated with the absorbed dose [19]. Dorn et al. [20] found that with lesion doses above 100 Gy were needed to ensure a complete response (CR) in their population of over 120 subjects treated for differentiated thyroid cancer. Jonsson and Mattsson [21] compared theoretical levels of activity that could be given to patients using patient-specific dose calculations and actual practice in nearly 200 cases of the use of radioiodine to treat Graves' disease at one institution. They showed that "most of the patients were treated with an unnecessarily high activity, as a mean factor of 2.5 times too high and in individual patients up to eight times too high, leading

to an unnecessary radiation exposure both for the patient, the family and the public." Pauwels et al. found a convincing relationship in their study of 22 patients with ^{90}Y Octreother [22] (an anti-somatostatin peptide) employing PET imaging with ^{86}Y to characterize the in vivo kinetics of the agent. In the treatment of thyroid cancer, treatments are mostly based on fixed activities rather than absorbed doses, although some have employed a dose-based approach [23, 24].

9.4.2 Other Diseases

I-131 meta-iodobenzylguanidine (mIBG) has been used for many years for the treatment of adult and pediatric neuroendocrine tumors, including pheochromocytoma, paraganglioma, and neuroblastoma. In studies in which dosimetry has been performed it has been shown that significant variations occur in absorbed doses to the whole body, normal organs, and tumors if a fixed administered activity approach is used [24, 25].

The use of monoclonal antibodies for the treatment of cancer, particularly the use of monoclonal antibodies (mAbs) against non-Hodgkin's lymphoma, has been widely studied [26–28]. Two products, Bexxar and Zevalin, employing an anti-CD20 antibody, have been approved by the United States Food and Drug Administration (US FDA) for the treatment of relapsed or refractory B-cell non-Hodgkin's lymphoma. Bexxar uses ^{131}I as the radionuclide, and Zevalin employs the longer-range beta emitter ^{90}Y. In the treatment with Bexxar, at least whole-body dose is evaluated with a target dose of 0.75 Gy [29] (which is really to limit marrow toxicity); with Zevalin, unfortunately, no dosimetry is performed [30]. Peptide therapy for neuroendocrine tumors has been investigated, primarily in Europe, including somatostatin analogues such as the compound DOTA-DPhe(1)-Tyr(3)-octreotide (DOTATOC). A few dosimetric studies have been performed [31–32]. Barone et al. [33] evaluated kidney dose from administrations of 8.1 GBq – 22.9 GBq of ^{90}Y DOTATOC and, calculating the BED instead of just absorbed dose, found a strong correlation between BED and creatinine clearance.

9.5 Conclusion

Our understanding of radiation biology from internal emitters requires considerable attention in the years to come. Improving this understanding can only come if careful dosimetry is performed with many therapy patients, as dose/effect relationships cannot be studied at all if there is no calculation of dose. Providing better and more durable outcomes for cancer patients requires more aggressive and optimized therapy, which again is not possible without careful and accurate dosimetry. A recent analysis [34] showed that:

- Widely accepted and automated methods, with relatively easy adjustment for patient-specific organ masses and use of individual patient kinetic data, are of similar cost and difficulty to those used in other therapeutic modalities.
- The use of a dosimetry-based approach will result in better patient outcomes, improving the quality of medical care for patients and reducing costs for the institutions involved.
- Careful use of patient-individualized dose calculations will produce calculated radiation dose estimates that correlate well with observed effects. Such data, as they accumulate with the increased application of patient-specific techniques, will continually improve our understanding of the link between radiation dose and effect, and the success rates of these techniques.

A paradigm shift is needed in the nuclear medicine clinic to accommodate these changes and improve patient therapy. The question is not *whether* we should perform individualized dosimetry for radionuclide therapy patients, but *how* we will perform it.

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