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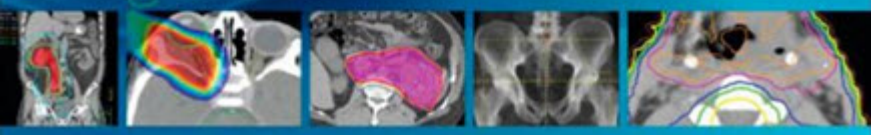
CLINICAL RADIATION ONCOLOGY

THIRD EDITION



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Dedication

To Katheryn, my wife and best friend, to our children and their spouses (Chad and Chrissy, Whitney and Jeff, Stacie and Nick, Ryan and Danna, Scott and Cindy), and to our grandchildren (Olivia and Adam; Rebecca, Andrew, Katie, and Matthew; Sam, Anna, Michael, and Ellie; Grant and Ian; Landon, Parker, and Rhys) for their love and support.

To my colleagues in Radiation Oncology, Surgery, Medical Oncology, Internal Medicine, Radiology, and Pathology for the opportunity to work together as a multidisciplinary team in the diagnosis and care of our patients.

LEONARD L. GUNDERSON

To my family, including Laurie, Miriam, Adam, Abigail, Agustin, Zekariah, Zohar, Sammy, Marcelo, Jonah, and Aurelio for the love and support they have given me for many years.

To my parents who taught me the importance of education, learning, and doing that which should be done.

To my many mentors who taught me in the past, and those who continue to teach me.

To my professional colleagues, both at the University of North Carolina and around the country, who have made me a better physician.

JOEL E. TEPPER

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Preface

The two prior editions of *Clinical Radiation Oncology* have been received very well by the radiation oncology community because of the focus and clear presentation, and it has become the standard radiation oncology textbook for many physicians. For the third edition of *Clinical Radiation Oncology*, the intent is to maintain the many excellent features of the prior editions while adding some new features, new chapters, and new Associate Editors and chapter authors. The most exciting new feature is that the third edition of *Clinical Radiation Oncology* will be available as an on-line version of the textbook (www.expertconsult.com) to those who purchase the hard-copy text. The on-line version will contain the entire hard-copy component of the textbook along with additional text, figures, tables, and several video clips.

The third edition again has separate sections on Scientific Foundations of Radiation Oncology, Techniques and Modalities, and Disease Sites. Within the section on Scientific Foundations of Radiation Oncology, a new chapter has been added on 'Survivorship and Late Effects.' In the section on Techniques and Modalities, the chapter on 'Conformal Therapy and Intensity-Modulated Radiation Therapy' has been expanded to include Image-Guided Radiation Therapy (IGRT), and Chapter 23, 'Metastatic Disease,' has been expanded to include a discussion of more aggressive treatment for subsets of patients with better-prognosis metastatic disease (i.e., solitary metastasis, oligometastases).

The section on Disease Sites now includes both new chapters and new authors. The Central Nervous System (CNS) Tumors component of the text includes a new chapter on 'Benign Brain Tumors.' In the Gastrointestinal Tumors component, the Gastric Cancer chapter has been expanded to include GE junction cancer.

The Associate Editors for Disease Sites chapters were an important component of the success of the two prior editions and have been maintained. Four new Associate Editors have been selected for the third edition: Dr. Minesh P. Mehta for Central Nervous System Tumors, Dr. Robert L. Foote for Head and Neck Tumors, Dr. Jeffrey A. Bogart for Thoracic Neoplasms, and Dr. Thomas A. Buchholz for Breast Cancer. Associate Editors are involved in the selection of chapter authors and in editing the chapters for scientific content and accuracy. In addition, for most Disease Sites, the Associate Editors wrote an Overview that allowed them to discuss issues common to various Disease Sites within the section and to give their unique perspective on important issues.

Features that are retained within Disease Sites chapters include an opening page format summarizing the most important issues, liberal use of tables and figures, a full-color format throughout each chapter and a closing section that has a treatment algorithm, reflecting the treatment approach of the authors, along with a discussion of controversies and problems. Chapters have been edited not only for scientific accuracy, but also for organization, format, and adequacy of outcome data (disease control, survival, and treatment tolerance).

We are again indebted to the many national and international experts who contributed to the third edition of *Clinical Radiation Oncology* as Associate Editors, senior authors, or co-authors. Their outstanding efforts combined with ours will hopefully allow this new edition to be a valuable contribution and resource in the coming years

Leonard L. Gunderson
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CHAPTER 1

Biologic Basis of Radiation Oncology

Elaine M. Zeman

WHAT IS RADIATION BIOLOGY?

In the most general sense, *radiation biology is the study of the effects of electromagnetic radiation on biologic systems*. Three aspects of this definition deserve special mention. First, "effects" may include everything from DNA damage to genetic mutations, chromosome aberrations, cell killing, disturbances in cell cycle transit and cell proliferation, neoplastic transformation, early and late effects in normal tissues, teratogenesis, cataractogenesis, and carcinogenesis, to name but a few. Second, "electromagnetic radiation" refers to any type of radiant energy in motion with wave and/or particulate characteristics that has the capacity to impart some or all of its energy to the medium through which it passes. The amount of energy deposited can vary over some 25 orders of magnitude, depending on the type of electromagnetic radiation. For example, 1-kHz radio waves have energies in the range of 10^{-11} to 10^{-12} eV, whereas x rays or gamma rays may have energies of 10 MeV or more. The more energetic forms of electromagnetic radiation, the so-called ionizing radiations, deposit energy as they traverse the medium by setting secondary particles in motion that can go on to produce further ionizations. Finally, "biologic systems" may be, for example, simple cell-free extracts of biomolecules or increasingly complex, from prokaryotes to single-celled eukaryotes, to mammalian cells in culture, to tissues and tumors in laboratory animals or humans, to entire ecosystems.

Radiotherapy-oriented radiobiology focuses on that portion of the electromagnetic spectrum energetic enough to cause ionization of atoms. This ultimately results in the breaking of chemical bonds that can lead to damage to important biomolecules. The most significant effect of ionizing radiation in this context is cell killing, which directly or indirectly is at the root of nearly all of the normal tissue and tumor responses noted in patients.

Cytotoxicity is not the only significant biologic effect caused by radiation exposure, although it will be the main focus of this chapter. Other important radiation effects, carcinogenesis, for example, will also be mentioned, although the reader should be aware that this aspect of radiation biology is a large discipline in and of itself, involving investigators from fields as diverse as biochemistry, toxicology, epidemiology, environmental sciences, molecular biology, tumor biology, and health and medical physics, in addition to those from the radiobiology field. Most radiation protection standards are based on minimizing the risks associated with mutagenic and carcinogenic events. Radiologic health professionals therefore are de facto educators of and advocates for the general public when it comes to ionizing radiation and need to be fully conversant in the potential risks and benefits of medical procedures involving radiation.

Most of this chapter will be devoted to so-called classical radiobiology, that is, studies that largely predate the revolution in molecular biology of the 1980s and 1990s. Although the reader might be tempted to view this body of knowledge as rather primitive by today's standards, relying too heavily on phenomenology, empiricism, and simplistic, descriptive models and theories, the real challenge is to integrate the new biology into the already-existing framework of classical radiobiology; this will be discussed in detail in Chapter 2.

RADIOTHERAPY-ORIENTED RADIOBIOLOGY: A CONCEPTUAL FRAMEWORK

Before examining any one aspect of radiobiology in depth, it is important to introduce several general concepts to provide a framework for putting the information in its proper perspective.

Therapeutic Ratio

The most fundamental of these concepts is what is termed the *therapeutic ratio*, in essence a risk-versus-benefit approach to planning a radiotherapy treatment regimen. Many of the radiobiologic phenomena to be discussed in this chapter are thought to play important roles in optimizing, or at least fine-tuning, the therapeutic ratio. In theory, it should be possible to eradicate any and all malignant tumors simply by delivering sufficiently high doses of radiation. Of course, in practice, the biologic consequences for normal tissues that are necessarily irradiated along with the tumor tissue limit the total dose that can be safely administered. As such, a balance must be struck between what is deemed an acceptable probability of a radiation-induced complication in a normal tissue and the probability of tumor control. Ideally, one would hope to achieve the maximum likelihood of tumor control that does not produce unacceptable normal tissue damage.

The concept of therapeutic ratio is best illustrated graphically, by making a direct comparison of dose-response curves for both tumor control and normal tissue complication rates plotted as a function of dose. Examples of this approach are shown in Figure 1-1, for cases in which the therapeutic ratio is either "unfavorable," "favorable," or "optimal," bearing in mind that these are theoretical curves. Actual dose-response curves derived from experimental or clinical data are much more variable, particularly for tumors, which tend to show much shallower dose responses.[1] This serves to underscore

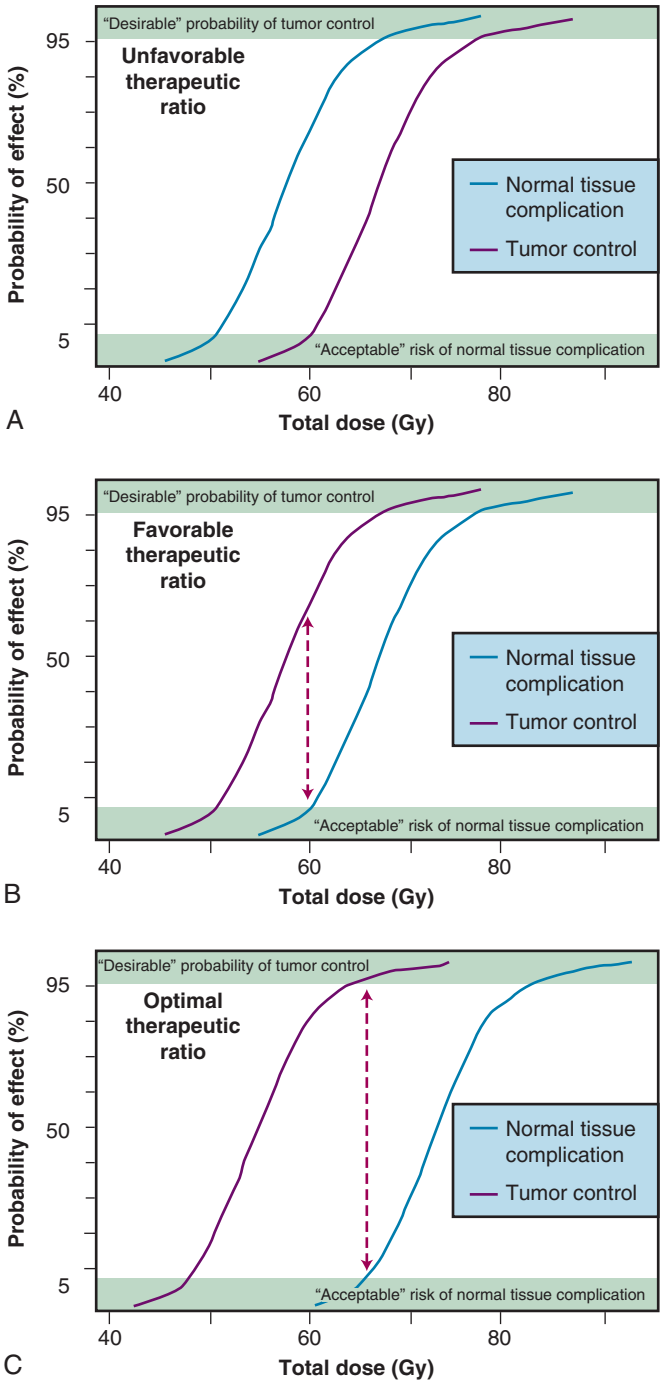

Figure 1-1 The graphs illustrate the concept of therapeutic ratio under conditions in which the relationship between the normal tissue tolerance and tumor control dose-response curves is unfavorable **(A),** favorable **(B),** and optimal **(C).**

how difficult it can be in practice to assign a single numerical value to the therapeutic ratio in any given situation.

Many of the radiobiologic properties of cells (and, therefore, tissues) can have either a favorable or an adverse effect on the therapeutic ratio. Therefore, in planning a course of radiation therapy, the goal should be to optimize the therapeutic ratio as much as possible, in other words, using our graphical approach, increase the separation between the tumor control and the normal tissue complication curves. This can be accomplished either by shifting the tumor control curve to the left with respect to the dose axis (toward lower doses for the same level of tumor control, that is, tumor radiosensitization) or by shifting the normal tissue complication curve to the right (toward higher doses for the same level of normal tissue complications, that is, normal tissue radioprotection) or perhaps a combination of both. The key is to shift these curves *differentially*, not necessarily an easy task given that there are precious few exploitable differences in the radiobiology of cells derived from tumors and those derived from normal tissues.

Radiation Biology "Continuum"

There is a surprising continuity between the physical events that occur in the first picosecond (or less) after ionizing radiation interacts with biologic material and the ultimate consequences of that interaction on tissues. The consequences themselves may not become apparent until days, weeks, months, or even years after the radiation exposure. Some of the important steps in this radiobiology "continuum" are listed in Table 1-1. The orderly progression from one stage of the continuum to the next—from physical to physicochemical to biochemical to biologic—is particularly noteworthy not only because of the vastly different time scales over which the critical events occur, but also because of the increasing biologic complexity associated with each of the endpoints or outcomes. Each stage of the continuum also offers a unique radiobiologic window of opportunity: the potential to intervene in the process and thereby modify all the events and outcomes that follow.

Levels of Complexity in Radiobiologic Systems

Another important consideration in all radiobiologic studies is the nature of the experimental system used to study a particular phenomenon, the assays used, and the endpoints assessed. For example, one investigator may be interested in studying DNA damage caused by ionizing radiation and, in particular, the frequency of DNA double-strand breaks (DSBs) produced per unit dose. As an experimental system, he or she might choose DNA extracted from mammalian cells. Then, using a DNA elution assay, the rate at which the irradiated DNA passes through a semipermeable membrane is measured as an endpoint and compared with the rate of elution of DNA extracted from cells that had not been previously irradiated. DNA containing more DSBs elutes faster than DNA containing fewer breaks, allowing a calibration curve to be generated that relates the dose received to the elution rate.

A second investigator, on the other hand, may be interested in improving the control rate of head and neck cancers with radiation therapy by employing a nonstandard fractionation schedule. In this case, the type of experiment would be a clinical trial. The "experimental system" would be a cohort of patients, some of whom are randomized to receive nonstandard fractionation, and the rest, standard fractionation. The endpoints assessed could be one or more of the following: locoregional control, long-term survival, disease-free survival, or normal tissue complication frequency, evaluated at specific times after completion of the radiation therapy.

In considering both the strengths and weaknesses of these two investigators' studies, any number of pertinent questions may be asked. Which is the more complex or heterogeneous system? Which is the more easily manipulated and controlled system? Which is more relevant for the day-to-day practice of radiation therapy? What kinds of results are gleaned from each, and can these results be obtained in a timely manner? In this example, it is clear that human patients

TABLE 1-1 Stages in the Radiobiology Continuum

Time Scale of Events ("Stage")	Initial Event	Final Event	Response Modifiers/Possible Interventions
10^{-16} to 10^{-12} second ("physical")	Ionization of atoms	Free radicals formed in biomolecules	Type of ionizing radiation; shielding
10^{-12} to 10^{-2} second ("physicochemical")	Free radicals formed in biomolecules	DNA damage	Presence or absence of free radical scavengers, molecular oxygen, and/or oxygen-mimetic radiosensitizers
1.0 second to several hours ("biochemical")	DNA damage	Unrepaired or mis-rejoined DNA damage	Presence or absence of functioning DNA damage recognition and repair systems; repair-inhibiting drugs; altering the time required to complete repair processes
Hours to years ("biologic")	Unrepaired or mis-rejoined DNA damage	Clonogenic cell death; apoptosis; mutagenesis; transformation; carcinogenesis; "early and late effects" in normal tissues; whole body radiation syndromes; tumor control; etc.	Cell-cell interactions; biologic response modifiers; adaptive mechanisms; structural and functional organization of tissues; cell kinetics; etc.

with spontaneously arising tumors represent a far more heterogeneous and complex experimental system than an extract of mammalian DNA. On the other hand, the DNA system is much more easily manipulated, possible confounding factors can be more easily controlled, and the measurement of the desired endpoint (elution rate) plus the data analysis can be completed within a day or two. Obviously, this is not the case with the human studies, where numerous confounding factors can and do influence results, manipulation of the system can be difficult if not impossible, and the experimental results typically take years to obtain.

The issue of relevance is an even thornier one. Arguably, both studies are relevant to the practice of radiation therapy insofar as the killing of cells is at the root of normal tissue and tumor toxicity caused by radiation exposure, and as cell killing usually is, either directly or indirectly, a consequence of irreparable damage to DNA. As such, any laboratory findings that contribute to the knowledge base of radiation-induced DNA damage are relevant. Clearly, however, clinical trials with human patients are not only a more familiar experimental system to clinicians but, also, their efficacy in cancer patients is, ultimately, the "gold standard" against which all new therapeutic strategies are judged.

All things considered, then, there is a time and place for both relatively simple systems and more complex ones. The relatively simple, homogeneous, and easily manipulated systems are best suited for the study of the mechanisms of radiation action, such as measuring DNA or chromosomal damage, changes in gene expression, perturbations of the cell cycle, or the clonogenic survival of cells maintained in culture. The more complicated and heterogeneous systems, with their unique endpoints, are more clinically relevant, such as assays of tumor control or normal tissue complication rates. Both types of assay systems have inherent strengths and weaknesses, yet both are critically important for hoped-for improvement in the practice of radiation therapy based on sound biologic principles.

Tissue Heterogeneity

Why is radiation therapy successful at controlling one patient's tumor but not another's, even when the two tumors seem identical? Why are we generally more successful at controlling certain types of cancers than others? The short answer to such questions is that although the tumors may appear identical "macroscopically," their component cells may be quite different phenotypically and/or genotypically. Also, there may be important differences between the two patients' normal tissues.

Normal tissues, being composed of more than one type of cell, are somewhat heterogeneous, and tumors, owing both to the genetic instability of individual tumor cells and to microenvironmental differences, are very heterogeneous. Different subpopulations of cells have been isolated from many types of human and experimental cancers, and these may differ in antigenicity, metastatic potential, sensitivity to radiation therapy and chemotherapy, and so on.[2,3] This heterogeneity is manifest within a particular patient, and to a much greater extent, between patients with otherwise similar tumors.

Both intrinsic and extrinsic factors contribute to this heterogeneity. Intrinsic factors may include the following: inherent radiosensitivity, gene expression, biochemical repair processes, modes of cell death (clonogenic versus apoptotic, for example), genomic instability, cell cycle kinetics, and the structural and functional arrangement of the tissue. Extrinsic factors, on the other hand, tend to be related to physiologic differences between tissues, such as the degree of vascularity, availability of oxygen and nutrients, pH level, energy charge, and proximity of, and degree of contact between, normal host tissue and the tumor.

What are the practical implications of normal tissue and tumor heterogeneity? First, if one assumes that normal tissues are the more uniform and predictable in behavior of the two, then tumor heterogeneity is responsible, either directly or indirectly, for most radiotherapy failures. If so, this suggests that a valid clinical strategy might be to identify the radioresistant subpopulation(s) of tumor cells and then tailor therapy specifically to cope with them. This approach is much easier said than done. Some prospective clinical studies now include one or more pretreatment determinations of, for example, the extent of tumor hypoxia[4] or the potential doubling time of tumor clonogens[5] as criteria for assigning patients to different treatment groups.

Another consequence of tissue heterogeneity is that any radiobiologic endpoint measured in an intact tissue is necessarily related to the radiosensitivities of all the subsets of cells, plus all the other intrinsic and extrinsic factors contributing to the overall response of the tissue. And, because data on normal tissue tolerances and tumor control probabilities are also

averaged among a number of patients, heterogeneity is even more pronounced.

"Powers of Ten"

Tumor control is achieved only when all clonogenic cells are killed or otherwise rendered unable to sustain tumor growth indefinitely. To estimate the likelihood of cure, it is necessary to know—or at least have an appreciation for—approximately how many clonogenic cells the tumor contains, how radiosensitive these cells are (i.e., some measure of killing efficiency per unit radiation dose), and what the relationship is between the number of clonogenic cells remaining after treatment and the probability of recurrence. The latter is perhaps the easiest to ascertain, given our knowledge of both the random and discrete nature of radiation damage and the general shape of dose-response curves for mammalian cells and tissues (approximately exponential for multifraction irradiation).

For a given number of surviving cells per tumor, the probability of local control can be derived from Poisson statistics using the equation $P = e^{-n}$, where P is the tumor control probability and n is the average number of surviving clonogenic tumor cells. For example, when, for a large number of tumors, an average of two clonogenic cells remain per tumor at the end of radiation therapy, the tumor control rate will be about 10%, that is, that nine out of ten tumors of the same size and relative radiosensitivity will recur. Should the treatment reduce clonogenic cell numbers to an average of 0.1 per tumor, the tumor control probability would increase to 90%; for 0.05 surviving cells per tumor, control would be 95%; and for 0.01 surviving cells per tumor, control would be 99%.

The tumor control probability for a given fraction of surviving cells is not particularly helpful if the total number of cells at risk is unknown, however, and this is where an understanding of logarithmic relationships and exponential cell killing is useful. Based on the resolution of existing tools and technology for cancer detection, let us assume that a 1-cm^3 (1-g) tumor mass can be identified reliably. A tumor of this size has been estimated to contain approximately 10^9 cells,[6] admittedly a theoretical value that assumes all cells are perfectly "packed" and uniformly sized and that the tumor contains no stroma. A further assumption, that all such cells are clonogenic (rarely, if ever, the case), suggests that at least 9 logs of cell killing would be necessary before any appreciable tumor control (about 37%) would be achieved, and 10 logs of cell killing would be required for a high degree of tumor control (i.e., 90%).

After the first log or two of cell killing, however, some tumors respond by shrinking, a partial response. After two to three logs of cell killing, the tumor may shrink to a size below the current limits of clinical detection, that is, a complete response. Although partial and complete responses are valid clinical endpoints, a complete response does not necessarily mean tumor cure. At least six more logs of cell killing would be required before any significant probability of cure would be expected. This explains why radiation therapy is not halted if the tumor "disappears" during the course of treatment; this concept is illustrated graphically in Figure 1-2.

Finally, it should be noted that while the goal of curative radiation therapy is to reduce tumor cell survival by at least nine logs, even for the smallest tumor likely to be encountered, it is much less clear how many logs of cell killing a particular normal tissue can tolerate before it loses its structural and/or functional integrity. This would depend on how the tissue is organized structurally, functionally, and proliferatively; which constituent cells are the most and least radiosensitive; and which cells are the most important to the integrity of the tissue. It is unlikely, however, that many normal tissues could tolerate a depletion of two logs (99%) of their cells, let alone nine or more logs.

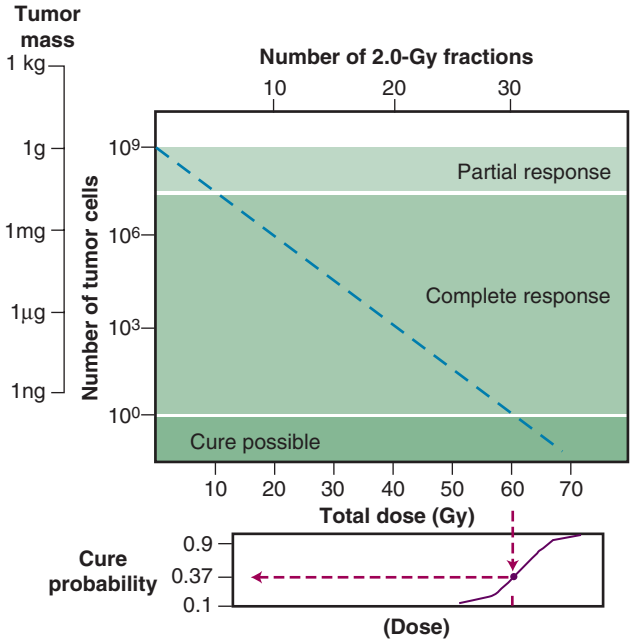

Figure 1-2 The relationship between radiation dose and tumor cell survival during fractionated radiotherapy of a hypothetical 1-g tumor containing 10^9 clonogenic cells. Although a modest decrease in cell surviving fraction can cause the tumor to shrink (i.e., partial response) or disappear below the limits of clinical detection (i.e., complete response), few cures would be expected until at least 9 logs of clonogenic cells have been killed. In this example, a total dose of at least 60 Gy delivered as daily 2-Gy fractions is required to produce a tumor control probability of 0.37, assuming each dose reduced the surviving fraction to 0.5.
Adapted from Steel G, Adams G, Peckham M, editors: The Biological Basis of Radiotherapy, New York, 1983, Elsevier.

RADIATION BIOLOGY AND THERAPY: THE FIRST 50 YEARS

In less than 4 years after the discovery of x rays by Roentgen,[7] radioactivity by Becquerel,[8] and radium by the Curies,[9] the new modality of cancer treatment known as radiation therapy claimed its first apparent cure of skin cancer.[10] Today, more than a century later, radiotherapy is most commonly given as a series of small daily dose fractions of approximately 1.8 to 2 Gy each, 5 days per week, over a period of 5 to 7 weeks, to a total dose of 50 to 70 Gy. Although it is true that the historical development of this conventional radiotherapy schedule was empirically based, there were a number of early radiobiologic experiments that suggested this approach.

In the earliest days of radiotherapy, both x rays and radium were used for cancer treatment. Because of the greater availability and convenience of using x-ray tubes and the higher intensities of radiation output achievable, it was fairly easy to deliver large single doses in short overall treatment times. Thus, from about 1900 into the 1920s, this "massive dose technique"[11] was a common way of administering radiation therapy. Unfortunately, normal tissue complications were quite severe. To make matters worse, the rate of local tumor recurrence was still unacceptably high.

Radium therapy was used more extensively in France. Because of the low activities available, radium applications involved longer overall treatment times to reach comparable total doses. Although extended treatments were less convenient, clinical results were often superior. Perceiving that the change in overall time was the critical factor, physicians began to experiment with the use of multiple smaller x-ray doses delivered over extended periods. At that time, there was already a radiobiologic precedent for expecting improvement in tumor control when radiation treatments were protracted.

As early as 1906, Bergonié and Tribondeau[12] observed histologically that the immature dividing cells of the rat testis showed evidence of damage at lower radiation doses than the mature nondividing cells. Based on these observations, the two researchers put forth some basic "laws" stating that x rays were more effective on cells that were: (1) actively dividing, (2) likely to continue to divide indefinitely, and (3) poorly differentiated.[12] Because tumors were already known to contain cells that not only were less differentiated but also exhibited greater mitotic activity, Bergonié and Tribondeau reasoned that several radiation exposures might preferentially kill these tumor cells but not their slowly proliferating, differentiated counterparts in the surrounding normal tissues.

The end of common usage of the single-dose technique in favor of fractionated treatment came during the 1920s as a consequence of the pioneering experiments of Claude Regaud and colleagues.[13] Using the testis of the rabbit as a model tumor system (because the rapid and unlimited proliferation of spermatogenic cells simulated to some extent the pattern of cell proliferation in malignant tumors), Regaud[14] showed that only through the use of multiple radiation exposures could animals be completely sterilized without producing severe injury to the scrotum. Regaud[15] suggested that the superior results afforded the multifraction irradiation scheme were related to alternating periods of relative radioresistance and sensitivity in the rapidly proliferating germ cells. These principles were soon tested in the clinic by Henri Coutard,[16,17] who used fractionated radiotherapy for the treatment of head and neck cancers, with spectacularly improved results. Mainly as a result of these and related experiments, fractionated treatment subsequently became the standard form of radiation therapy.

Time-dose equivalents for skin erythema published by Reisner,[18] Quimby and MacComb,[19] and others[20,21] formed the basis for the calculation of equivalents for other tissue and tumor responses. By plotting the total doses required for each of these "equivalents" for a given level of effect in a particular tissue, as a function of a treatment parameter such as overall treatment time, number of fractions, dose per fraction, and so on, an isoeffect curve could be derived. All time-dose combinations that fell along such a curve would, theoretically, produce tissue responses of equal magnitude. Isoeffect curves, relating the total dose to the overall treatment time, derived in later years from some of these data,[22] are shown in Figure 1-3.

The first published isoeffect curves were produced by Strandqvist[23] in 1944, and are also shown in Figure 1-3. When transformed on log-log coordinates, isoeffect curves for a variety of skin reactions, and the cure of skin cancer, were drawn as parallel lines, with common slopes of 0.33. These results implied that there would be no therapeutic advantage to using prolonged treatment times (i.e., multiple small fractions versus one or a few large doses) for the preferential eradication of tumors while simultaneously sparing normal tissues.[24] It was somewhat ironic that the Strandqvist curves were so popular in the years that followed, when it was already known that the therapeutic ratio *did* increase (at least to a point) with prolonged, as opposed to very short, overall treatment times. However, the overarching advantage was that these isoeffect curves were quite reliable at predicting skin reactions, which were the dose-limiting factors at that time.

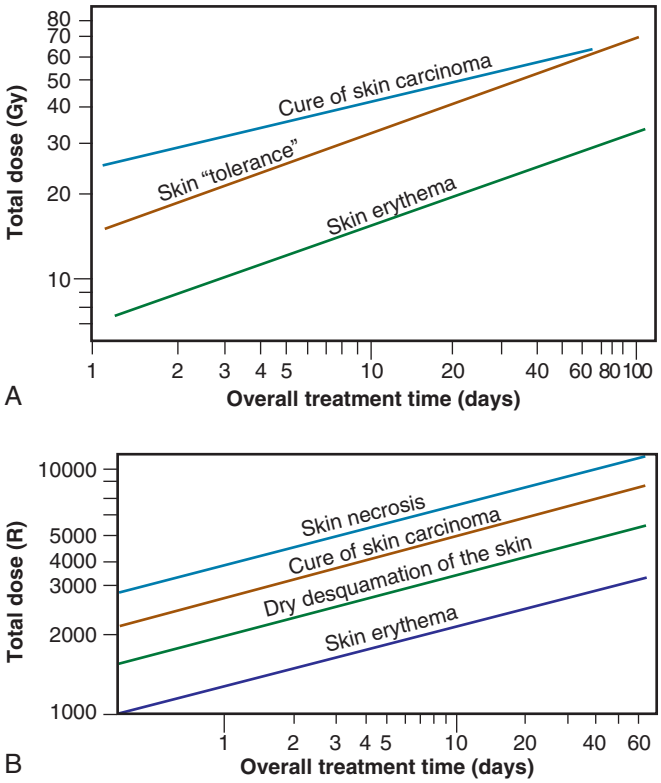

Figure 1-3 Isoeffect curves relating the log of the total dose to the log of the overall treatment time for various levels of skin reaction and the cure of skin cancer. **A,** Isoeffect curves were constructed by Cohen on the basis of a survey of earlier published data on radiotherapy equivalents.[21-26] The slope of the curves for skin complications was 0.33, and the slope for tumor control was 0.22. **B,** The Strandqvist[28] isoeffect curves were first published in 1944. All lines were drawn parallel and had a common slope of 0.33.
A, *Adapted from Cohen L: Radiation response and recovery: Radiobiological principles and their relation to clinical practice. In Schwartz E, editor: The Biological Basis of Radiation Therapy, Philadelphia, 1966, JB Lippincott, p 208;* ***B,*** *adapted from Strandqvist M: Studien uber die kumulative Wirkung der Roentgenstrahlen bei Fraktionierung, Acta Radiol Suppl 55:1, 1944.*

THE "GOLDEN AGE" OF RADIATION BIOLOGY AND THERAPY: THE SECOND 50 YEARS

Perhaps the defining event that ushered in the golden age of radiation biology was the publication of the first survival curve for mammalian cells exposed to graded doses of ionizing radiation.[25] This first report of a quantitative measure of intrinsic radiosensitivity of a human cell line (HeLa, derived from a cervical carcinoma[26]) was published by Puck and Marcus[25] in 1956. To put this seminal work in the proper perspective, however, it is first necessary to review the physicochemical basis for why ionizing radiation is toxic to biologic materials.

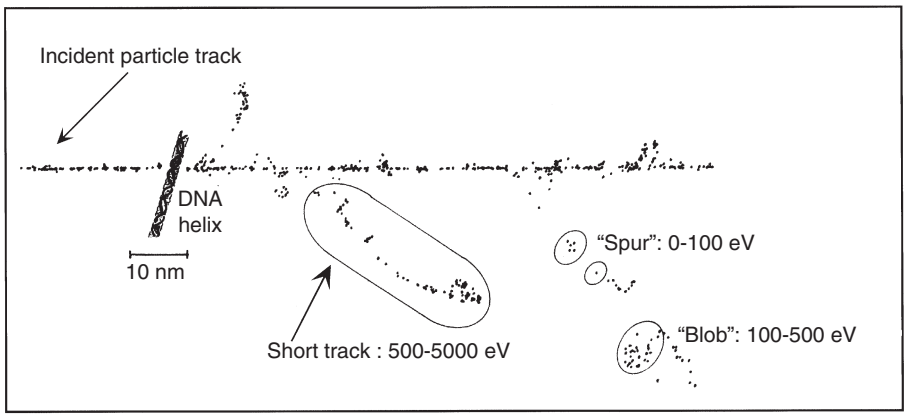

Figure 1-4 Hypothetical alpha particle track through an absorbing medium, illustrating the random and discrete energy-deposition events along the track. Each event can be classified according to the amount of energy deposited locally, which determines how many ionized atoms will be produced. A segment of a DNA double helix is shown approximately to scale.
Adapted from Goodhead D: Physics of radiation action: microscopic features that determine biological consequences. In Hagen U, Harder D, Jung H, et al, editors: Radiation research 1895-1995, proceedings of the 10th international congress of radiation research, vol. 2. congress lectures, Wurzburg, 1995, Universitatsdruckerei H Sturtz, p 43.

The Interaction of Ionizing Radiation with Biologic Materials

As mentioned in the introductory section of this chapter, ionizing radiation deposits energy as it traverses the absorbing medium through which it passes. The most important feature of the interaction of ionizing radiation with biologic materials is the random and discrete nature of the energy deposition. Energy is deposited in increasingly energetic packets referred to as "spurs" (100 eV or less deposited), "blobs" (100 to 500 eV), or "short tracks" (500 to 5000 eV), each of which can leave from approximately three to several dozen ionized atoms in its wake. This is illustrated in Figure 1-4, along with a segment of (interphase) chromatin shown to scale. The frequency distribution and density of the different types of energy deposition events along the track of the incident photon or particle are measures of the radiation's linear energy transfer or LET (see also the "Relative Biologic Effectiveness" section, later). Because these energy deposition events are discrete, it follows that although the average amount of energy deposited in a macroscopic volume of biologic material may be rather modest, the distribution of this energy on a microscopic scale may be quite large. This explains why ionizing radiation is so efficient at producing biologic damage; the total amount of energy deposited in a 70-kg human that will result in a 50% probability of death is only about 70 calories, about as much energy as is absorbed by drinking one sip of hot coffee.[27] The key difference is that the energy contained in the sip of coffee is uniformly distributed, not random and discrete.

Those biomolecules receiving a direct hit from a spur or blob, receive, relatively speaking, a huge radiation dose, that is, a large deposition of energy in a very small volume. For photons and charged particles, this energy deposition results in the ejection of orbital electrons causing the target molecule to be converted first into an ion pair and then into a free radical. Further, the ejected electrons—themselves energetic charged particles—can go on to produce additional ionizations. For uncharged particles such as neutrons, the interaction is between the incident particles and the nuclei of the atoms in the absorbing medium, causing the ejection of recoil protons (charged) and lower-energy neutrons. The cycle of ionization, free radical production, and release of secondary charged particles continues until all the energy of the incident photon or particle is expended. These interactions are complete within a picosecond after the initial energy transfer. After that time, the chemical reactions of the resulting free radicals predominate the radiation response (discussed later).

Any and all cellular molecules are potential targets for the localized energy deposition events that occur in spurs, blobs, or short tracks. Whether the ionization of a particular biomolecule results in a measurable biologic effect depends on a number of factors, including how probable a target the molecule represents from the point of view of the ionizing particle, how important the molecule is to the continued health of the cell, how many copies of the molecule are normally present in the cell and to what extent the cell can react to the loss of "working copies," and how important the cell is to the structure or function of its corresponding tissue or organ. DNA, for example, is obviously an important cellular macromolecule and one that is present only as a single double-stranded copy. On the other hand, other molecules in the cell may be less crucial to survival yet are much more abundant than DNA, and therefore have a much higher probability of being hit and ionized. The most abundant molecule in the cell by far is water, comprising some 80% to 90% of the cell on a per weight basis. The highly reactive free radicals formed by the radiolysis of water are capable of adding to the DNA damage resulting from direct energy absorption by migrating to the DNA and damaging it indirectly. This mechanism is referred to as "indirect radiation action" to distinguish it from the aforementioned "direct radiation action."[28] The direct and indirect action pathways for ionizing radiation are illustrated below.

Direct effect

$$\mathrm{DNA} \underset{\text{(irradiate)}}{\rightarrow} [\mathrm{DNA^{+} + e^{-}}] \underset{\text{(ion pair)}}{\rightarrow} \underset{\text{(DNA free radical)}}{\mathrm{DNA^{\bullet}}}$$

Indirect effect

$$\mathrm{H_2O} \underset{\text{(irradiate)}}{\rightarrow} [\mathrm{H_2O^{+} + e^{-}}] \underset{\text{(ion pair)}}{\rightarrow} \underset{\substack{\text{(other}\\ \text{radical}\\ \text{reactions)}}}{\rightarrow} {}^{\bullet}\mathrm{OH} + \mathrm{DNA} \rightarrow \underset{\substack{\text{(DNA free radical}\\ \text{and water)}}}{\mathrm{DNA^{\bullet} + H_2O}}$$

The most highly reactive and damaging species produced by the radiolysis of water is the hydroxyl radical (•OH),