RADIATION ONCOLOGY

Rationale, Technique, Results

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Preface

The fourth edition of this text brings a critical revision of every chapter, including many needed major changes, and a new chapter on the radiotherapy of children. Much outdated material has been replaced with current concepts and new illustrations.

Dr. Hector Battifora, a surgical pathologist, has joined Dr. Brand and me as a co-author and has contributed generously to the fourth edition. His input has improved the quality of the discussions as well as the illustrations.

The change in the title from *Therapeutic Radiology* to *Radiation Oncology* is in keeping with the original aim outlined in the preface to the first edition: to serve as an introduction to selected clinical problems in cancer care and to express a philosophy of radiotherapy that will lead to improved patient care. Rationale, technique, and results are covered, as well as the problems in diagnosis and the value of competitive techniques. The change in title is also in keeping with the expanding goals of our specialty, which include not only the administration of radiations but also the entire spectrum from diagnosis to clinical management, treatment, and follow-up care. Obviously, all aspects of the specialty cannot be presented in this small volume, but a clinical orientation directed toward improved care of patients with cancer has guided us in our selection of ideas and clinical data.

We wish to thank our many friends of the Northwestern University Medical Center who contributed their data and ideas. Especially do we wish to thank Ms. Nikki Litteria for her endless patience and good spirits in helping us prepare and complete the manuscript.

William T. Moss

Contents

Chapter 1

Introduction to radiation oncology

The beginning of radiotherapy was no different from that of any other medical specialty. A dependable method of measuring tissue dose was not available; even if it had been, optimum dose-time relationships were not understood. The physical and biologic mistakes that were certain to follow were often fatal. Recurrences from underirradiation and necroses from overirradiation were the natural consequences of this ignorance. Cancers totally unsuited for radiotherapy were irradiated by physicians who had almost no understanding of the tool they were employing. Unlike many modalities used in medicine, an early evaluation of the results of irradiation is never possible. Mistakes in judgment often cannot be recognized for years. Once a decision is made to change a faulty technique, case material must be accumulated, the patients must be treated, and the results of treatment must be followed; this, too, takes many years. Because of this time-consuming process of evaluation, every patient treated should be considered a research prospect and all possible clinical and physical data recorded to make future evaluations more meaningful. It may take hundreds or even thousands of patients with a specific type and clinical stage of cancer to detect meaningful differences in morbidity or survival between two techniques. In a lifetime no single physician may see such a volume of patients. To detect such differences within a reasonable time and thereby speed technical improvement, promising joint collaborative efforts involving many institutions have been developed. The formation of the Radiation Therapy Oncology Group (RTOG) is a major step in providing the means for valid clinical trials. The radiation oncology community is looking to such group efforts for many answers. However, this must limit neither individual initiative nor clever innovations, which are the real spark of progress. Most important is that we remember that the protocol cannot relieve us of the responsibility of caring for each patient as an individual each day.

DEFINITION OF RADIATION ONCOLOGY

The administration of ionizing radiations to patients is only a part of the specialty of radiation oncology. The evaluation of patients for irradiation, care during irradiation, and posttreatment care and follow-up examinations are vital

to good radiotherapy, which, of course, means good patient care. Such a specialty demands a thorough knowledge of the disease in question, a knowledge of the efficacy of alternative methods of treatment, an appreciation of the clinical aspects of radiophysiology and radiobiology, and a knowledge of the pertinent physical characteristics of the radiations employed. There is no single text containing all of this material. However, the clinical behavior of most malignant diseases has been discussed admirably by Ackerman and del Regato. A variety of excellent summaries of the basic radiobiologic aspects of clinical radiation therapy are now available (Cohen; Fowler, 1966; Deeley and Wood; Rubin and Casarett; Pizzarello and Witcofski). The practical physical problems encountered in patient treatment are discussed by Johns and Hendee. There are many other good texts that have contributed significantly to the resident's training. However, after reviewing all these standard texts and reading the current journals, the student of radiation oncology often finds it difficult to correlate the data and to be able to do more than juggle isodose curves in accordance with someone else's recipe. It is our belief that once the growth characteristics of cancer are understood and the radiation tolerances of the associated normal tissues are appreciated, the techniques of irradiating the *volume of interest* (the volume to be considered for irradiation; see p. 30) are relatively simple. For this reason we have emphasized the rationale rather than the details of technique. This should not mislead one to conclude that we believe technique is unimportant. On the contrary, as discussed on p. 31, care and precision in technique are vital to good patient care.

GENERAL CONCEPTS IN RADIATION ONCOLOGY

There is nothing worse in cancer therapy than being half certain of the diagnosis and then treating the patient halfway. This not only delays adequate treatment, but also prejudices future adequate irradiation. The diagnosis must be proved if at all possible. Then full treatment is undertaken with an accepted risk. If the diagnosis cannot be proved, one must proceed with the most likely diagnosis. If, after weighing the data, it is decided that irradiation is indicated, the dosage should be as if the suspected diagnosis were proved. In the same vein, irradiation can rarely remedy all the harm resulting from ill-advised surgery. All too often patients are referred to the radiation oncologist after having been told by the surgeon: "We took out all we could and we are going to add a little irradiation to finish the job." Irradiation given after such inadequate surgery is at times the best possible course, but it is rarely tolerated as well or is as effective as irradiation given without preceding surgery. Half treatment with surgery and half treatment with irradiation never add up to one successful treatment. This should not be confused with planned combined irradiation and surgery.

High-dose radiation therapy of large volumes is usually associated with rather well-defined risks related to normal tissue damage. Reductions of these risks by

improving dose-time relationships, beam quality, and precision of technique have been major steps in our progress. However, the fear of serious normal tissue damage is the most common cause of undertreatment. A horrible frustration comes to all oncologists when they recognize that cancer is recurring because of their attempt to spare the patient morbidity.

In addition to its curative usefulness, radiotherapy is one of the most valuable palliative tools available. Many cancers that are not curable by any means are made to regress or are held in check by irradiation. Infected, bleeding cutaneous or mucosal ulcers may be made to heal, obstructing pressure-producing masses can be made to shrink, and painful bone-destroying metastases can be made to regress. In fact, the great palliative value of radiotherapy sometimes masks its curative usefulness. The large proportion of obviously hopelessly ill patients whose suffering is relieved by radiotherapy must not lead the radiation oncologist to lose sight of the curative possibilities of his modality. However, the tremendous palliative value of radiotherapy results in an association of radiotherapy with inoperability or even incurability that is difficult to overcome.

Inoperability per se is never an indication for irradiation. Patients with inoperable cancer deserve an assessment of tumor site and extent, cell type, and aim of palliation. This should be done carefully and deliberately. Furthermore, the pathologist's report alone cannot guide one to a decision relative to the indications for irradiation. Even the more resistant cell types may be helped by irradiation in certain circumstances, whereas the more undifferentiated cell types may not always benefit from irradiation. The referring physician may suggest the use of radiotherapy for the psychologic boost it imparts to patients who are terminally ill. Faking radiation therapy or giving radiation therapy for psychologic reasons alone is poor psychotherapy and even worse radiotherapy. The physician must accept his real responsibility in the care of these terminal patients. Cytotoxic agents such as radiations must not be administered with the hope of rendering some vague psychotherapeutic effect. To avoid the unnecessary association of our armamentarium with failure, the radiation oncologist should select his patients for palliative treatment just as carefully as he selects those for curative treatment. To withhold treatment that will likely relieve suffering is inexcusable, but to administer irradiation with no hope of producing relief is likewise the practice of poor medicine. In the selection of patients for irradiation, it is much more difficult to withhold than to administer radiotherapy. As in any other field, it often takes wide clinical experience coupled with courage to render the best patient care. It may sound paradoxical, but palliative irradiation usually requires more mature judgment and more personal involvement by the radiation oncologist than does curative irradiation.

A big step will have been taken when radiation oncology can be placed on a completely rational basis. It will not only be more teachable, but it will also be relieved of some of its uncertainty and the mysticism that is occasionally associated with it. Even though progress is slow, much empiricism has already been

removed. The reasons for radiotherapeutic successes and failures are becoming more obvious. The limitations of various techniques have been clarified, and improved techniques have been improvised. Data on the efficacy of irradiation in malignant diseases and their various types of spread are being collected. The inadequacy of our present methods of collecting clinical data is appreciated more widely, and efforts are being made to obtain comparable series of patients treated by competitive methods. A tremendous volume of such work must be carried out to clarify the many unsettled clinical problems in radiation oncology.

In the chapters that follow, the various classical results as well as results of recent series are cited. The statistical validity of these results may be justifiably challenged. However, such data must serve as the radiation oncologist's guide until better figures become available.

Similarly, a statement of optimum dose can almost always be criticized because of obvious inaccuracies. Optimum doses, by necessity, are based on clinical experiences extending back as long as 20 years ago. In this period, dosimetry was crude by contemporary standards. Many of the dosage guides now used for cancer control and normal tissue response are based on these data. Radiation oncologists have nothing better from which to extrapolate for today's optimum techniques. These limitations must not be passed on to the next generation of radiation oncologists. The computer-aided techniques show us the magnitude of heterogeneity of dose within the volume of interest. Precise treatment planning assists in delivering the desired dose to the selected volume. The importance of the size of the fractions, number of fractions, and volume encompassed is recognized as being as significant as the total number of days and the total dose. With this precision, knowledge of tumor response and normal tissue response can be used more effectively to increase cure rates and decrease sequelae.

No attempt will be made to outline the details of the ideal training program for the radiation oncologist. It is clear that such training should include experience in an active cancer clinic. The resident should have a continuous association with a clinically oriented radiation physicist and with a surgical pathologist sympathetic to the radiation oncologist's problems. The basic concepts and clinically applicable aspects of radiobiology should be taught throughout the training period. The teaching and service relationships to the surgeon and chemotherapist are obvious. Most important of all is supervision by a radiation oncologist who is capable of inspiring the trainee. Aside from conducting patient care as described, this teacher must coordinate the contributions from other participants in the training program.

Relationship between surgical pathologist and radiation oncologist. Without expert guidance from a well-qualified surgical pathologist, all cancer therapy, whether radiotherapeutic, surgical, or chemotherapeutic, will be on uncertain ground. Without such guidance the radiation oncologist will be uncertain as to what he is treating and, if he cures the patient, he will not know what he has

cured or why he has been successful. In addition, the microscopic cell type is frequently critical in determining whether the treatment will be surgical, radiotherapeutic, chemotherapeutic, or a combination. If the treatment is to be irradiation, the microscopic diagnosis will be one of the more important factors determining the time-dose-volume relationships. If the diagnosis were malignant lymphoma rather than well-differentiated squamous cell carcinoma, we would advocate more generous fields and lower total doses. A careful gross and microscopic examination of the surgical specimen is a good measure of the adequacy of excision. The diagnosis of "inadequate excision" may well justify vigorous irradiation with a curative aim before there are clinical signs of recurrence. If the impression of the pathologist is that the excision has been adequate, careful follow-up with no irradiation may be the best policy.

It is imperative that a close collaboration exist between the pathologist and the radiation oncologist. The pathologist should convey to the radiation oncologist his findings in more detail than simple pathologic coding. Not only must he describe cell type and degree of differentiation, but also the type of invasive growth and presence or absence of vascular permeation. The type of host response to the tumor is also an important contribution to treatment planning. Since standard nomenclature is not uniformly agreed on, even by pathologists themselves, the pathologist must make every effort to clarify his interpretation, especially in uncommon cases. A candid and open-minded approach is necessary when dealing with cases of doubtful or controversial nature. The need for further diagnostic measures and the means by which to obtain them can then be mutually agreed on.

Aside from these immediate contributions of the surgical pathologist to the conduct of clinical radiotherapy, it is through careful study of autopsy and operating room material that the radiation oncologist can learn the origin, routes of spread, and extent of infiltration and metastases. He learns the frequency with which certain lymph node groups will be involved and thus can justify treatment or no treatment of specific volumes on such data. He discovers the reasons for treatment failure and may change his technique to remedy the defects. The pathologist, better than anyone else, can assist the radiation oncologist in defining tolerances of deep tissues and high dose sequelae.

If the radiation oncologist is fortunate enough to have a pathologist sympathetic to his problems, he must be aware of the pathologist's capabilities and understand what he means by his interpretations. Frequent discussions of problems with the pathologist will assist him in understanding them and will enable him to contribute greatly to patient care. This type of cooperative approach permits the pathologist to realize the satisfaction of playing a more direct role in patient care.

Relationship between surgeon and radiation oncologist. With rare exception, the cure of cancer depends on radiotherapeutic or surgical treatment. The basic cancer training for both surgeons and radiation oncologists consists of studying

the types of cancers, their routes of invasion and metastases, methods of treatment, and causes of failure. One cannot evaluate a patient's problem and recommend a form of treatment unless one is well acquainted with the possibilities of alternative methods of treatment. For many types of cancers, such as the adenocarcinomas of the large bowel, it is agreed that radical surgery offers the patient the best chance of control of the disease. For other sites, such as carcinomas of the nasopharynx, for medulloblastomas, and for most localized lymphomas, radiotherapy is unquestionably superior. However, there is a large group of lesions, particularly in the oral cavity, larynx, and pharynx, in which control rates of the two methods have been reported to be nearly equal. Neither method is preferred in all these sites. With such patients the working relationship between surgeon and radiation oncologist must be close. Each such patient should be examined and evaluated by both specialists prior to treatment. Pretreatment discussions are highly informative and offer the best chance for true collaboration in the treatment of cancer. Before the surgeon or radiation oncologist can properly recommend the best form of treatment, each must be well acquainted with the possibilities of both surgery and radiotherapy. Through such discussions each specialist will have greater respect for the other's problems and for the possibilities for cure by the other's modality, and each will be in a position to evaluate his own modality more accurately.

A combination of irradiation and surgery is used with advantage in several sites and in several different ways. In the treatment of seminoma of the testicle, the primary lesion is removed and the iliac and aortic nodes are irradiated. For carcinomas of the anterior two thirds of the tongue, this combined form of treatment is reversed—the primary lesion is irradiated and the cervical nodes are excised. In the treatment of carcinoma of the endometrium, both modalities are applied to the same volume. These various types of combined treatment are discussed in more detail later. They demand that each specialist have confidence in the other's ability and that each have an understanding of the other's intentions.

Each specialist will have treatment failures in patients who may then be cured or palliated by the other modality. This referral of patients and its associated admission of failure humble both the surgeon and the radiation oncologist, and as a result they tend to work more closely together. (See Chapter 2 for a discussion of radiotherapy and surgery.)

Relationship between physicist and radiation oncologist. The variation of tissue response with both quantity and quality of radiations has led to a close relationship between the radiation oncologist and the radiation physicist. The development of more effective treatment techniques and of a variety of sources of radiations has been a result of this collaboration. It has also increased our dependency on the physicist. Physics training for the radiation oncologist is essential if he is to apply his tools in the most effective manner. This training should enable him to apply standard techniques without serious errors in proposed total

dose or dose distribution and without danger to himself or his staff. However, such training must of necessity be limited. For this reason it is essential to have a clinically inclined physicist in the department to consult during the development of new techniques and to solve the many physical problems associated with unusual situations in existing techniques. Unfortunately, there are far too few such physicists to consult, and most radiation oncologists are therefore limited strictly to their own knowledge of physics.

The development of computer aids for dosimetry provides practical means for detailed dosimetry in most commonly encountered clinical situations in both external beam and intracavitary and interstitial techniques. However, computer usage demands input from both the physicist and the radiation oncologist if serious pitfalls are to be avoided. The dosimetrist, long an integral part of the treatment planning team in England, is now recognized as an almost indispensable member of the radiation oncology staff in the United States. This individual, whether a physicist, a physicist's assistant, or a radiotherapy technician with special training, is a critical link in the precise administration of radiations to patients.

Relationship between internist and radiation oncologist. With rare exception the cure of cancer is dependent on irradiation or surgery. However, the cancer patient often seeks the internist's advice before the diagnosis is made. The cancer-conscious internist often has the responsibility of making an early diagnosis, and it is to him and to the clinician in family practice that we must look for major progress in shortening the interval from onset to diagnosis. If these clinicians are acquainted with the indications for irradiation and the characteristics differentiating good from poor radiotherapy, they can refer cancer patients in a direction that will assure their most effective care.

Patients in age periods in which cancer most commonly occurs also have a relatively high incidence of cardiovascular, pulmonary, and renal diseases. Not infrequently the successful administration of radiations will depend on simultaneous treatment for these degenerative diseases. The internist can provide vital help with his special knowledge of hematology, infectious diseases, and circulatory and renal diseases. During such collaborative efforts each physician must at all times appreciate the other's aims. It is for these reasons that the internist must not only appreciate good radiotherapy, but also work with the radiation oncologist. The reverse is equally true.

It should be emphasized here that a loose collaborative association between a radiologist who is not clinically inclined and a referring physician depending on the radiologist to conduct therapy will lead to frequent undertreatment or overtreatment. There must be a continuous collaboration between the internist and the radiation oncologist if the patients with both cancer and degenerative disease are to receive the benefit of good medical care.

Relationship between medical oncology and radiation oncologist. The specialty of medical oncology also requires a wide knowledge of the natural

history of various types of cancer. To select patients for chemotherapy requires a knowledge of the relative value of radiotherapy and surgery. Obviously such a well-trained physician is the third member of the treating team. The shortage of well-trained physicians in this area leaves much of the chemotherapy to others not prepared to approach therapy with the same attitude as the surgeon and the radiation oncologist.

More often than not, chemotherapeutic agents follow or are given simultaneously with radiotherapy. Many chemotherapeutic agents damage the hemopoietic tissues. This may limit radiation therapy. The reverse is equally true. Other tissues, such as the bowel epithelium, the skin, the epithelium of the oral cavity, and bladder mucosa may be damaged by both cytotoxic chemicals and radiations. Combinations of radiations and chemotherapy must be planned with care lest the competition for normal tissue tolerance limit the benefit of either modality alone.

RADIOBIOLOGIC CONCEPTS IN CLINICAL RADIATION ONCOLOGY

The clinically important physiologic and morphologic changes produced by the actions of radiations are presented in the discussions of each tumor type. No review of these changes need be presented here. However, certain radiation-induced changes common to all cells and tissues and certain concepts important in discussing clinical radiation responses are pertinent. The abbreviated description to follow is intended to assist in the understanding of some clinical radiation therapy practices. The reader is referred to Pizzarello and Witcofski and to Fabrikant for more detailed accounts of the effects of radiations on cells.

Cellular radiation responses. Radiation-induced changes in tissues and organs are the sum of changes in the constituent cells. The various types of cells found in a given tissue show similar patterns of response provided the cells are in comparable phases of their growth cycle and have comparable growth cycles. Many malignant and nonmalignant mammalian cells can be grown and studied in tissue culture with a technique similar to that used for bacteria (Puck and Marcus). In such studies the cell's reproductive capability is used as a measure of its viability and growth potential. Thus the number of colonies or clones that grow after irradiating a known number of viable cells is an index of the radiosensitivity of the reproductive mechanism. The typical cell survival curve plots the percentage of cells surviving against various doses of radiations (Fig. 1-1). The slope of the curve varies with the radiosensitivity of the particular cell type, its environment during irradiation, the type and the method of administration of radiations, and the biologic state of the cells. This curve has a characteristic "shoulder" followed by a straight line. The more resistant the cell, the broader the shoulder and the less steep the slope. The shoulder represents the accumulation of hits or sublethal injuries.

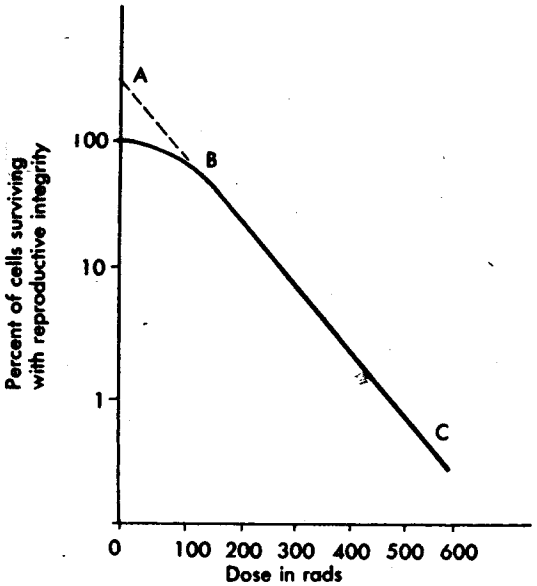

Fig. 1-1. Typical cell survival curve. The proportion of cells retaining their reproductive activity after a given dose of radiations is plotted. A curve is drawn through the series of points obtained with various doses. The slope of BC varies with radiosensitivity of the particular cell type and its environment during irradiation. The length of the line from A to the 100% survival point is apparently a measure of the number of targets in a cell that must be hit within a relatively short period of time to cause cessation of reproduction.

When considering the injurious effects of radiations, cells are pictured as containing certain critical structures that play a vital role in their reproductive capacity. These structures are called *targets* and are generally accepted as being DNA molecules in genes. Radiation-induced damage to a DNA molecule (target) may trigger a sequence of serious cellular changes. However, if this type of DNA damage occurs singularly, it is rapidly repaired. Mammalian cells have several such targets, which must be hit within the same short period to end cellular reproduction. By contrast haploid cells such as bacteria require only one hit. The shoulder of the cell survival curve (Fig. 1-1) is a graphic demonstration of this accumulation of sublethal, repairable damage to critical targets in mammalian cells. With a single low dose very few mammalian cells will have all targets hit. Therefore survival will be high. With a higher dose most cells will have some critical targets hit. Some will have all targets hit and only they will fail to reproduce. Finally, with still higher doses, many cells will have accumulated sufficient hits in a short period of time so that only one additional hit will be necessary to destroy reproductive capacity. At this dose and above, the relationship between dose and reproductive capacity is exponential, that is, it is shown by a straight line on a semilog plot.

The shape of the shoulder depends in part on the number of critical targets in the cell. This number of targets is determined by extrapolating up along the straight part of the curve to the point of intersection with the ordinate (Fig. 1-1). The length of the ordinate between this intersection and the 100% survival point is called the *extrapolation number* and is a measure of the average number of critical targets in each cell. The number of critical targets varies with physiologic conditions, presence or absence of oxygen in the cell, phase of the cell in its life cycle, and unknown factors.

Radiosensitivity and radioresponsiveness. The radiosensitivity of cells in a culture is expressed by the slope of the cell survival curve (Fig. 1-1). It is also expressed in terms of D_0, that is, the single dose of radiations necessary to kill 63% of the cells using the straight part of the curve. The magnitude of intracellular repair is measured by the broadness of the shoulder denoted by D_q (Fig. 1-5). However, these definitions are not readily applied to the clinical situation.

From the clinical standpoint the terms *radiosensitive* and *radiosensitivity* have been used in such a variety of circumstances that a single definition is not possible. Radiosensitivity, when used clinically, most often refers to the relative radiation-induced change toward a given end-point (usually a decrease in tumor size or altered cellular or organ function) produced by a given dose-time-volume relationship. In view of the definition as related to cell culture experiments, this term is no longer used to describe clinically observed changes. We agree with Andrews that the term *radioresponsiveness* is more appropriate. Radioresponsiveness refers to the rate of gross tumor shrinkage and anatomic or functional changes. The clinical determination of the relative radioresponsiveness of a tissue implies some type of comparison. In this regard there are no established standards of response and comparisons are made within the entire spectrum of cancers and normal tissues.

One of the more confusing clinical uses of the term radioresponsiveness is in regard to the relative rate of radiation-induced shrinkage of a cancerous mass or of a normal organ. A cancerous mass or a normal organ shrinks when cell death and absorption exceed new cell production. At least three cellular changes are necessary. Mitosis must be slowed or arrested. At the same time the existing nonmitotic cells may or may not die at an increased rate and they must be absorbed. Shifts in any or all of these rates may modify the rate of tumor shrinkage. Cell turnover rates of the irradiated cells are important determinants. In some cancerous masses such as large nodes in the neck, a high proportion of the cells are necrotic, nearly necrotic, or not proliferating. In such a situation, where circulation is poor, this necrotic tissue may not be removed for months. If dead cells occupy a large proportion of the tumor, the tumor may shrink very little, even if all of the remaining cells are killed. Other factors that modify shrinkage of a cancer are integrity of phagocytic processes and rate of proliferation of the cancer cells or normal cells between fraction. Thus the rate of shrink-

age of a cancerous mass may be misleading if it is regarded as an index of radiosensitivity. The possibility of a poor correlation between rate of tumor shrinkage and ultimate control of a cancerous mass has been stressed by Suit and associates, and by Fazekas and associates. Yet it must be emphasized that large masses with extensive necrosis are the most likely to remain indurated at the completion of radiotherapy and are the most likely to have persistent viable cancer. It is not surprising, therefore, that clinical support exists relative to the prognostic significance of persistent induration at the completion of irradiation. Indeed, this constitutes the radiobiologic justification for *boosting doses* that are delivered to residual masses after large-port irradiation.

In a normal organ with a recognized cell renewal system there is a spectrum of cellular radioresponses. These responses are related to the proliferative activity of the cells in question, that is, whether they undergo mitosis frequently, occasionally, only after unusual stress, or never. The same spectrum of cells exists in cancers. The response of a given cancer to irradiation is related to the proportion of cells ordinarily destined to undergo early and frequent mitosis as well as the proportion that is destined to a long survival in a more mature nonmitotic state. Bergonie and Tribondeau described this fact in 1906 in their "law," which states that the effect of radiations on cells is proportional to the cells' functional and morphologic differentiations.

It is not likely that the current fractionation scheme of 150 to 200 rads per day, 5 days a week to a total dose of 6,000 to 6,500 rads is optimal for all types of squamous carcinoma. Preirradiation knowledge of cellular kinetics of each cancer could assist in tailoring a more efficient fractionation. However, even within a given patient, metastasis may show different doubling times and the doubling time in a given metastasis may increase as it enlarges. Thus the practical use of cell kinetics in tailoring optimum fractionation patterns is not yet within reach.

The slope of the cell survival curve varies with the cellular oxygen tension (Fig. 1-2). Both in vitro and in vivo studies confirm that for a given lethality anoxic cells require two to three times the dose required for well-oxygenated cells (Fig. 1-3). The ratio of the former dose to the latter is called the oxygen enhancement ratio (OER); its importance is found in the fact that cell clusters of more than a few millimeters in diameter undoubtedly contain hypoxic cells. Because of their decreased radiosensitivity, hypoxic tumor cells could account for a proportion of local cancer persistences. To enhance the effect of radiations, dissolved oxygen must be in the cell near the site of the radiation-produced free radical. The enhancement is presumed to be a consequence of oxygen combining directly or indirectly with free radicals split from critical cell targets by radiations. In this way oxygen reduces the chances that recombination of free radicals with critical targets will occur and thus reduces the chances of restoring the integrity of the critical targets. From a practical standpoint the enhancement is effective over a limited range of oxygen partial pressures (Fig. 1-2).