Progress in
RADIATION THERAPY

VOLUME II

Edited by FRANZ BUSCHKE, M.D.

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with 17 contributors

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In Memoriam

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Contents

Introduction

By FRANZ BUSCHKE

PERHAPS THE GREATEST COMPLIMENT paid to the first volume of *Progress in Radiation Therapy* was the statement of one reviewer that it is ". . . rather . . . aimed at those of us who are interested in radiation therapy as a way of life." The question may, of course, be asked whether anybody who does not consider radiation therapy as a way of life should practice a specialty which deals almost exclusively with a fatal disease where the success or failure of the initial treatment quite commonly decides the patient's fate.

Consistent with the policy outlined in the "Introduction" to the first volume, the editor has again selected for discussion in this second volume ". . . problems of fundamental biological, physical, or clinical importance which have immediate application to clinical radiation therapy." The gulf is still too wide between the practice of radiation therapy as a mere physical science on the one hand and, on the other hand, as a routine execution of standard procedures prescribed in a radiotherapeutic cookbook that lists "cancerocidal" doses for standardized disease entities, neatly catalogued and placed in cubby holes. Efforts to improve our understanding of the *basic* biologic, pathologic, and clinical problems—and even our pondering these problems at leisure—may help to narrow this gulf.

A few of the problems previously discussed have again been included—some in order to view them from a different aspect, others for more detailed consideration of particular phases.

The increasingly more general use of super- and megavolt therapy makes our understanding of TISSUE TOLERANCE of the deeper structures and of parenchymatous organs ever more important. Lampe's critical review of the radiation tolerance of the central nervous tissue in the first volume is now followed by an analysis of the *tolerance of the kidney* by Luxton and by Kunkler, as well as Parker's study of the *tolerance of bone and cartilage under conditions of clinical therapy*. Because of misconceptions regarding the hazards of radiation chondritis and necrosis associated with irradiation of lesions overlying cartilage and bone, many patients, particularly those with lesions around the eyelids and the nose, are subjected to unnecessarily extensive plastic surgical procedures. Exaggerated fear of "unavoidable" radiation damage to bone and cartilage results from a widespread lack of appreciation of the fact that many such damages are

related to what are now considered erroneous techniques of treatment and that such disasters can be avoided rather consistently if treatment is given with correct indications and technique—particularly with sufficient protraction and with the use of the proper quality of rays. Parker's personal clinical experience permits him to integrate *relevant* experimental data with clinical observations. Thus, he reaches sound, rather definite conclusions for the recognition of those situations in which clinically significant damage to cartilage or bone can be consistently avoided, as contrasted with those in which such damage is an almost unavoidable risk and must be weighed accordingly in making a therapeutic decision.

Discussions related to PHYSICAL AND TECHNICAL PROGRESS were intentionally omitted from the first volume in order to restore the balance by greater emphasis on biologic and clinical problems. Because of the extensive discussion of technical modalities in medical meetings and publications, this phase has again been de-emphasized in this volume. The place of supervolt radiation is now fairly well established and its superiority from the point of better tissue tolerance and lower morbidity acknowledged—except by those unbiased by experience. In most situations, an insistence on using mediumvolt therapy today is equivalent to recommending surgery with the carbolic acid spray.

However, increased interest in the use of *Cesium-137* as a source of external irradiation prompted the editor to include in this volume Botstein's and Schulz' analysis of their experience, based on observations of more than 200 patients who were consistently treated by this modality during a 2 year period.

Of the fundamental BIOLOGIC problems which are of immediate importance for clinical radiation therapy, the question of the relative radiobiologic effectiveness which was acute a few years ago can be considered as having been answered satisfactorily for all clinically important purposes by the thorough analysis by Kohn in the first volume. The most urgent problems at this time are related to the fractionation and protraction of treatment in time (time-dose relationship), the influence of chemical alterations of the *milieu* on the radiation effect, and the question of the superiority of homogeneous vs. inhomogeneous irradiation.

The importance of a better understanding of the *dependence of the radiation effect on the distribution of dose in time* with regard to tumor response and tolerance of normal tissues was emphasized in the first volume and discussed in two chapters, by du Sault and by Baclesse. The question of the effect of other than the classic daily fractionation has become more urgent for two reasons:

First, with the use of shorter wave length radiation, much larger daily doses are tolerated well, and preliminary observations seem to indicate

that fractionation by two or three weekly treatments with correspondingly high single doses (but with the more usual over-all protraction) may in certain situations be as effective (and perhaps in some situations even more so) as daily treatment, and would be more economical.

Second, investigations with treatment under increased oxygen tension (see below) make it likely that, if such a procedure can ever be considered for clinical purposes, daily therapy would be impractical. A better understanding of the effect of other forms of fractionation which may be practical under these circumstances is, therefore, imperative. Botstein has used *fractionations other than daily treatments* for several years, and his experience encourages further investigation.

In his contribution on modification of radiation effects by chemical means in the first volume, Patt briefly discussed what was then known with regard to the effect of *increased oxygen tension*. Since then, this problem has been investigated more thoroughly in several institutions particularly from the viewpoint of practical possibilities and the effect on human tumors. A critical review of the present situation seemed timely. We are fortunate to have Peter Wootton's contribution which is based on a critical analysis of the literature and on the author's personal experiences gained from a recent visit to most of the British and American institutions in which this problem is being studied systematically.

There has been an increasing interest in the COMBINATION OF RADIATION THERAPY WITH EITHER SURGERY OR CHEMOTHERAPY. The improvement of both radiological and surgical techniques has made the *planned combination of radical radiation therapy with radical surgery* possible without the previously not acceptable risk and without significant increase in morbidity and complications. The rationale for such a planned combined approach differs with different situations: in some advanced differentiated epitheliomas of the oral cavity, in which even with the most radical acceptable operation the surgical margin might be dangerously narrow, the purpose of radical preoperative irradiation is to sterilize the peripheral (presumably more radioresponsive) portion of the primary tumor and thus to provide in effect a wider surgical margin beyond neoplastic involvement.[3, 4] The combination has proved to be useful for some carcinomas of the palate, pillar or floor of mouth, but has only rarely improved the chances in advanced carcinoma of the tongue. This rationale is obviously invalid in the treatment of neoplasms that tend to invade lymphatics diffusely, e.g., tonsil. In other situations where recently combined therapy has been applied more systematically (e.g., bronchus [2] and esophagus [8]), the rationale is different and the likelihood of success more phoblematic: the sterilization of lymph nodes in anatomic areas unsuitable for block dissection. The effect of the peripheral portion of the primary tumors is more incidental

in these situations, although occasionally a primarily technically inoperable lesion has apparently been rendered operable.[2] Further investigations of such combined procedures, executed in institutions with a well integrated and thoroughly cooperating radiotherapeutic and surgical team, are clearly indicated. In view of this increased interest, the comprehensive review of all types of combined radiotherapeutic and surgical procedures by Bloedorn seemed useful as a baseline for further investigation.

From the point of view of investigative interest, public appeal and more widespread use, CHEMOTHERAPY is growing in importance, even though, so far, its legitimate clinical indications (as accepted by serious chemotherapists) remain rather limited. It is unfortunate that the legitimate hope and the frantic search for a "cure for cancer" tends to encourage premature publication of observations with every new "drug du jour." Publications of what were really only steps in the process of investigation have at times been misinterpreted, resulting in the indiscriminate use of some chemotherapeutic agents and thereby depriving the patient at times of treatment by more predictable, time-tested procedures. We may perhaps meditate on the fact that Ehrlich did not publish the 605 unsuccessful attempts which finally led to "606"—Salvarsan. Neither should we forget that it was not necessary to conduct complex statistical cooperative studies to convince even the most skeptical disbeliever that Salvarsan, insulin or the antifolics were effective and represented decisive progress in the treatment of syphilis, diabetes and acute leukemias, or that, for that matter, radiation therapy has made significant contributions in the control ("cure") of some forms of neoplasms. In these situations, the accumulated body of previous experience has served as a convincing control.

This is not meant to minimize the importance of well controlled investigations, but rather *to epitomize the necessity for strict identification of that which is still purely investigative in nature.*

Some quite sincere, though inaccurate, claims for chemotherapeutic agents are based on insufficient appreciation of the time-tested, consistent accomplishments of competent radiation therapy. Other erroneous claims —particularly regarding the effect of combined chemo- and radiation therapy—derive from an insufficient allowance for the vagaries of radiation response and from the illusion that the response of individual tumors to certain doses or irradiation can be reliably predicted. This became quite apparent in the remarks by some of the clinical radiation therapists who participated in the Session on Research and Radiotherapeutic Approaches to Chemical Sensitization at the informal conference in Carmel, California, in 1960.[17] It was pointed out, for instance, that bronchial carcinoma is not a good test object for the evaluation of combination therapy because of its great variability in response to irradiation. Most examples published to demonstrate the response to relatively small doses of irradia-

tion if used in combination with chemotherapy can be matched by similar observations of comparable regression following irradiation alone, using similar doses. Even in epidermoid carcinomas of the oral cavity or pharynx, the response of the individual tumor is unpredictable and surprises in either direction are not uncommon. We are also becoming increasingly aware that some mesenchymal malignant neoplasms, and even some melanomas, respond much more readily to radiation therapy than the text books would have us to believe.[9, 21]

The increased interest in and the growing importance of chemotherapy obviously make a basic understanding of its present relative status as important for the clinical radiation therapist as is a fundamental appreciation of the indications for and limitations of cancer surgery. In spite of the voluminous literature—or perhaps because of it—it therefore seemed desirable to include in this volume a critical re-evaluation of the relative place of chemotherapy and radiation therapy, with proper appreciation of the dependence of results on techniques. Dr. Papac's own extensive experience with discriminately used chemotherapy and her long, close association with radiation therapy, both in the Royal Marsden Hospital and in our institution, provide the background for her critical analysis.

Dr. Papac's general review is followed by three inter-related contributions on *Hodgkin's disease* by Noetzli and Sheline, Vaeth, and Crosbie. Analysis of the material treated by x-ray therapy alone, both at the University of California Hospitals in San Francisco, where for many years low-dose techniques had been used, and at the Swedish Hospital in Seattle, where during the last 20 years tumor doses of about 3500 r. were consistently employed, permits a long term evaluation of results obtained by radiation therapy alone with different techniques and demonstrates the importance of the consideration of technical details for valid conclusions regarding the accomplishments of radiation therapy. This provides a firmer foundation for an evaluation of the relative indications for radiation therapy vs. chemotherapy and of the most effective radiotherapeutic techniques.

The two most commonly encountered errors in the treatment of Hodgkin's disease are either the use of a too rigidly standardized radiation technique without proper adjustment to the individual situation or, at the other extreme, a rather haphazard form of therapy without any valid conception of the natural course of the disease in the particular patient. In spite of the great complexity and variation of the disease, certain rather well documented experiences permit us to recognize some guiding principles:

1. Certain forms of Hodgkin's disease progress rather slowly and remain limited for many years to one body segment (for instance, in one upper quadrant or a supradiaphragmatic portion of the body). Others

represent already generalized disease when the first symptoms appear. I believe that Crosbie's suggested classification somewhat facilitates our understanding here. The primary generalized forms (Class III of Crosbie's classification) should be separated from the generalized late *stages* of disease which had started as Class I or II. Furthermore, we frequently find that the difference between "anatomic generalization" (involvement of many widely separated lymphatic areas) without constitutional symptoms and "constitutionalized disease" (with clinically predominating constitutional symptoms, such as fever, malaise and marked weight loss) is not sufficiently appreciated from the point of prognosis and therapy.

2. It has been demonstrated satisfactorily that the radiation therapy in disease limited to one or two regional areas (Classes I and II) should be vigorous enough to prevent recurrence in previously treated foci. The contributions included here have again demonstrated that for this purpose doses of 3500 to 4000 r. are necessary and that the incidence of recurrence within the first year increases with decreasing dose. It seems that the local recurrence is not only undesirable because of the difficulty and strain of repeated treatment, but that such recurrence shortens the over-all life span of such patients because it weakens the host's resistance to the disease. This is suggested by the lower 5 year survival in Crosbie's series of Class II (in patients who had more frequent recurrences in insufficiently treated areas) compared to his Class I and to Peters' Class II [13] (both more vigorously treated). Vaeth's demonstration of marginal mediastinal recurrences and Crosbie's analysis of failure in Class II indicate the need for treatment of a sufficiently large *contiguous* volume. The necessity for careful attention to this requirement is obvious from the repeated observations of recurrences in gaps between treated volumes. For certain types of Hodgkin's disease, a technique recently recommended by Kaplan which encompasses several neighboring regional areas in one large, contiguous volume, is undoubtedly sound.[10]

3. The relative place of radiation therapy and chemotherapy has become fairly well defined by now, although we still too frequently encounter a rather indiscriminate and haphazard practice. Chemotherapy is contraindicated in regional disease (Classes I and II). It is also of only very limited value in the late generalized stages of a disease which originally began as regional (Class I or II), even if it may offer temporary palliation. Its most important life-prolonging indication is in Class III, when the disease is primarily too generalized anatomically for vigorous x-ray therapy, but when the general condition is still such that the disease is not considered as terminal.

Radical radiation therapy is an all-or-none procedure, as is radical cancer surgery. An initial error in judgment or technique can rarely be

corrected and RETREATMENT following *radical* therapy is contraindicated. This old classic adage of Coutard's still stands despite the more refined technical facilities now available. However, with the increasing number of installations for radiation therapy, and particularly since Cobalt-60 therapy has become more readily available without a corresponding increase in the number of qualified radiation therapists, we see more and more patients who were *inadequately* treated, for whom we may make a last desperate attempt to correct the situation by using techniques which must be individually adjusted to the treatment of such iatrogenically changed cancer. This can be a considerable challenge to the experienced radiotherapist.

Since the need for this kind of therapy has increased significantly during the recent years and since reports about this aspect of radiation therapy are singularly scarce, I have asked Dr. Simon Kramer to contribute a review of *indications, techniques and results of retreatment,* based on his own experiences.

The growing recognition that some supposedly "radioresistant" tumors —particularly some mesenchymal neoplasms which are often difficult to classify—may show an "unexpected" and at times clinically significant radiation response [9, 21] re-emphasizes the necessity of recognizing the *limitations of histological diagnosis.* Thus, it must be realized that the pathologist's diagnosis does not always provide the final and unequivocal answer but must be correlated with all other findings. A systematic discussion of the entire problem of the validity of histological diagnosis seemed to be long overdue. We are therefore grateful to Dr. Oscar Rambo for his original and comprehensive study.

In the introduction to the first volume, it was emphasized that "progress in radiation therapy is of more than academic interest only if the results of such progress are made available to the majority of patients with cancer." This requires a much greater number of thoroughly trained, specializing radiation therapists than are now available, the establishment of more training centers, and a greater awareness of the place of radiation therapy in the treatment of cancer among the medical profession. Based on the expected number of new cancer patients per year, it can be estimated that about 1500 radiation therapists are needed in this country. The 1962 edition of the Roster of the American Club of Therapeutic Radiologists, which includes almost all radiologists whose practice is limited to radiation therapy, lists 159 members in the United States.[1, 15] In this respect, it is interesting to note that in Russia, a broad plan to expand cancer service calls for the training of 2000 radiotherapists between 1960 and 1965.[19]

To attain these objectives, the most important basic requirement still

remains the recognition of radiation therapy as a clinical specialty, with an appreciation of its true scope. In this respect, some significant and most encouraging steps indicating progress can be recorded:

1. The National Institutes of Health, in 1961, inaugurated a new broad "program for the encouragement of radiotherapy research and training activities."

2. Harvard University, in conjunction with the American Cancer Society and its Massachusetts division, has established "The Allan T. and Viola E. Fuller—American Cancer Society professorship of radiology . . . to further strengthen teaching and research in radiotherapy." [20]

These two steps are only the more dramatic expressions of a general change in atmosphere. More medical schools have established sections of radiation therapy with a permanent staff of full time radiotherapists. The requests for well trained therapists to staff such sections, both in medical schools and in some of the newly established departments of radiation therapy in large metropolitan hospitals, steadily increase. Some schools have begun to offer separate programs for resident training in radiation therapy. This question was discussed at a symposium on "The Immediate Separation of Training in Diagnostic and Therapeutic Radiology" at the meeting of the Association of University Radiologists in Palo Alto in May 1961. Since July 1961, Stanford University has been accepting only trainees for either radiation therapy or x-ray diagnosis and has abandoned the training of "general radiologists." At the University of California School of Medicine, San Francisco, since July 1960 residents have been accepted either for training in radiation therapy (3 years), x-ray diagnosis (3 years), or general radiology (4 years). The difficulty in attracting residents for these programs in radiation therapy—consistently predicted for years by the supporters of general radiology—has so far not materialized in either of these institutions.

Training of radiation therapists side by side with general radiologists has, of course, led to some organizational difficulties, but it appears to have some merit at this time for three reasons:

1. General radiologists are still needed.

2. The training of general radiologists side by side with trainees in radiation therapy gives the general radiologist a better appreciation of his limitations and of the difference between a general radiologist and a specializing radiation therapist.

3. Service in the section of radiation therapy frequently provides the first exposure of the general radiologist to radiation therapy since, to date, radiation therapy has usually been inadequately represented in the undergraduate medical curriculum and during internship. Such exposure has induced some trainees who started as general radiologists to discover an

interest in radiation therapy and to switch to this specialty. During the last year, we have had in our department six conversions of residents originally accepted for general radiology—three requested to change to the therapy program; three to the diagnostic program.

In this process of gradual emergence of radiation therapy as one of the recognized clinical specialties, some hazards should be recognized:

1. This development should not be accelerated too greatly. In the first place, there are not yet enough radiation therapists available who are truly qualified to establish the field in an authoritative and competent fashion so as to create confidence among the other specialists and practitioners in a community. Del Regato [14] has pointed out that the creation of departments of radiation therapy without such adequate staffing would amount to delivery without gestation.

2. Much as we desire a complete separation of radiation therapy from x-ray diagnosis, long accepted in Great Britain, the Scandinavian countries and France, it seems that in our economic structure general radiologists are still needed for service in smaller communities. Many patients requiring repeated and not critical therapy are often cared for more easily in their home communities (for instance, those with lymphomas, metastatic diseases, etc.). The practice of radiation therapy by general radiologists, however, should not be considered as a solution which is desirable in principle, but as a matter of expediency and compromise. For metropolitan areas where specialized radiotherapeutic services are readily available, to the best of this writer's knowledge, no valid medical reason for the perpetuation of this only historically justified situation has been advanced. General radiologists should therefore be taught to realize the limitations of their competence in radiation therapy and to recognize that critical therapy for curable carcinoma should be referred to qualified radiation therapists or to larger centers, somewhat comparable to the situation facing general surgeons in such communities who will send patients in need of critical cardiac or cranial surgery elsewhere. This is increasingly recognized, and a frank statement like that in a recent editorial in *Radiology* [7] indicates encouraging progress: "One does not lose stature by securing for his patients a better deal than he can give by virtue of limited up-to-the minute medical knowledge or a limited experience or limited facilities." In view of the importance of this problem, the editor requested Dr. Patrick Lynch to contribute a chapter describing his experiences with *radiotherapeutic service in a smaller community.*

3. A third hazard which should be avoided is the attempt to make all programs for the teaching of radiation therapy follow the same pattern. The present (sound and desirable) interest in *radiobiology* and the corresponding emphasis on *research* have led some to a philosophy which

considers clinical radiation therapy almost as an annex to radiobiology (which would be comparable to considering surgery as an annex to pathology). Until recently, radiation therapy has not had a good chance to develop freely: It was first smothered by surgery, then by physics, then by the worship of machinery, then by chemotherapy, and we should now avoid the risk of having it smothered by an overemphasis on radiobiologic research.

Experimental investigation and clinical observations have been closely interrelated and mutually stimulating from the very beginning. The classic studies of Regaud and Lacassagne [16] on the effects of irradiation on the testicle laid the foundation of successful radiation therapy by their influence on the direction of Coutard's clinical investigations. Conversely, "for a long period . . . the main avenues of experimental radiobiology were conceived and initiated by observations made in applying radiations to the treatment of disease in man. And though radiobiology applied to radiation therapy is still carried on, this is not the immediate objective in the greater share of radiation studies now in progress." [5] The present relationship between radiobiologic research and clinical radiation therapy was well epitomized in the remarks with which Lampe summarized his impressions at the conclusion of the joint meeting of radiobiologists and radiotherapists [11]:

> I consider it of value to expose those of us who are solely clinical radiotherapists to the kind of radiobiological material discussed . . . If it does nothing else, it informs regarding the complexities of the problems involved. For the clinical therapist, the gap between current radiobiologic knowledge and the questions posed by the problems encountered in clinical work is so great as to be quite discouraging, and must make the clinician aware that he must still seek solution of some of his problems at the level of clinical investigation.

Obviously it is desirable that some training programs emphasize radiobiologic research. But it should be recognized that clinical radiation therapy is not merely radiobiology applied to the human mammal any more than it is radiation physics applied to the human phantom. An insistence that all programs be patterned after the same fashion with the main emphasis on research may eliminate some of the most excellent academic and nonacademic training centers in the country, centers from which most of the now available radiation therapists have emerged. While, obviously, a sound background in radiobiologic understanding should be as integral as pathology and physics to every training program, the need for institutions which provide thorough training in clinical radiation therapy should still be recognized. Such institutions should not be expected to change their basic philosophy and atmosphere by appointing members to their staffs for the specific purpose of "doing research" in