From virtually every perspective the future of radiation oncology for the next three decades must be reckoned of high promise. One of the most positive facts underlying this statement is the exceptional quality of young physicians entering this discipline. Certainly, in terms of academic credentials, we have never had such talent to choose from in the resident selection process. The contrast between our present situation and that of three decades ago could hardly be sharper. Then, there were small numbers of resident candidates, few quality teaching programs, only occasional research programs and a modest literature. Today, the scene is qualitatively and quantitatively better, and the prospects are for this improvement in professional staffing at all levels to continue.

Radiation oncology is in the midst of a period of rapid and profound change affecting nearly every facet of our discipline. In the near future there will be (1) important advances in technical proficiency resulting in the ability to use substantially smaller treatment volumes with proof that the target is within that treatment volume; (2) subspecialization within radiation oncology that will become the standard in large centers and practice groups; (3) radiation oncology subspecialists integrated with their subspecialty counterparts in surgery, medical/pediatric oncology, radiology, and pathology to form site-specific teams for patient management; (4) increasing combinations of radiation with chemotherapy and/or surgery; (5) a rationalized integration of agents to modify responses of tumor and/or normal tissues, e.g., chemotherapeutic agents, biological response modifiers, cytokines; (6) the use of new predictors of response of tumor and normal tissues so as to permit individualized, scientifically-based treatment strategies; (7) sustained efforts to reduce costs of care, i.e., manage our practices much more efficiently and reduce costs; and (8) at more distant times, inclusion of molecular-genetic-based therapy into management protocols.

National manpower requirements for all medical specialists are being revised downward. As part of this process, reductions in the number of residents in radiation oncology are currently being implemented. This may be appropriate and have long-term beneficial consequences for oncology.
However, serious consideration will have to be given to the increase in physician time in planning and implementing definitive treatments as the technical developments described below are introduced into clinical practice.

There are several significant negatives for our future, and they are all economic. The changing health care system in this country will effect reductions in the available funds for patient care, research and development, and education. This result will be to slow but not stop the gains projected above. A significant decrement in the economic status of the radiation oncologist and to a lesser degree radiation physicists, therapists, and nurses is almost certain.

Still, my long-term view of radiation treatment quality is clearly optimistic. This may not obtain over the short term in the United States as we modify our current health care system. The near certainty that radiation treatments can be made more effective will force development and implementation of new methods. Medicine and science are international; even though we in the United States may experience a slowing of the pace of development, we can confidently expect to gain significant amounts of knowledge from laboratory and clinical studies throughout the world. For the pessimists, an examination of the advances which occurred in the 1930s, a decade of severe economic depression, may bring some encouragement. These include the introduction of supervoltage X-ray machines, van de Graaff accelerators, and betatrons to limited clinical use. Past neutron therapy trials were begun. There were major gains in diagnostic imaging during this same period.

Several of the anticipated changes will be considered here. For this paper, the plan is to discuss advances which seem certain to be realized and then those judged likely. Finally, comments will be offered on the probable consequences for radiation oncology of the exuberant growth of the field of molecular biology and the potential for its successful applications to oncology.

**TECHNOLOGICAL ADVANCES AND THEIR IMPACT**

An astounding series of technological advances are appearing on the radiation oncology scene and will enhance the quality of treatment. There will, of course, be some increase in cost and especially in time required of the physician in treatment planning. Most of these technical developments stem from (1) astonishing advances in computer power at steeply declining costs, which will yield vastly more effective software systems for treatment planning; (2) the appreciation of the clinical importance of smaller treatment volumes to patient outcomes; and (3) dramatic improvements in diagnostic imaging techniques. Several of the most important are here discussed.

**Three-dimensional optimized treatment planning software**

The concept for three-dimensional (3-D) conformal optimized treatment planning came from and has been clinically tested in academic departments. These software systems are under intensive development by major industrial firms, often in collaboration with the academic centers.

Treatment planning using mature 3-D software systems and state-of-the-art computers will demand significantly more of radiation oncologists’ time. Although it may appear counterintuitive, the time required of the clinical physicist for the individual patient’s plan will decrease, a reversal of the present planning efforts. The actual planning process for a definitive or radical treatment is expected to proceed according to the following steps. First, the treatment position will be selected and an immobilization device prepared which will permit a highly-reproducible setup with severely restricted motion of the patient during each treatment session. Then a treatment planning imaging study (e.g., computed tomography [CT] or magnetic resonance [MR] imaging) will be performed with the patient immobilized in the treatment position. Following this, the physician
will define the boundaries of the targets (initial, intermediate, and final) and of each of the sensitive normal tissues of concern on each section of the CT/MR images. In addition, the physician will indicate the allowance to be made for patient/target motion. The dose constraints for each of the designated normal tissues and dose aims for the target will next be specified. This information would be transferred by a physicist/treatment planner into the treatment planning software program on a powerful computer able to construct a series of beams—gamma and/or electron—to cover the target with minimal margins. Next, the planning system will generate many hundreds of plans in the process of optimizing the dose distribution. For the planning, the system will be able to consider static and dynamic beams, noncoplanar, dynamic wedges, intensity modulation, inverse planning, etc. The yield being the best feasible dose distribution, that is, adequate dose constraints on normal tissues with achievement of an effective dose to target. Further, the uncertainty around each isodose contour will be displayed. The computer will submit several of the supposedly best plans for the clinician and physicist to review. These plans would be produced in a mere few minutes, as computer capabilities will continue to advance. By the end of this century every large treatment center is expected to have a computer the equivalent of the so-called “supercomputer” of just a few years ago. Dose distributions will be shown as the dose volume histogram for any desired organ or tissue or portions thereof. These systems will provide the clinician and clinical physicist with means of interactively viewing and comparing the computer’s first offering of plans.

This treatment planning procedure will be enhanced by the inclusion of subroutines to display not only the physical dose distributions but also the predicted biological effect distribution. Several groups are developing this capability. The clinician and clinical radiation biologist select values for the parameters of alpha/beta ratio, cell proliferation kinetics, etc., for each specific tissue of concern. There will be, of course, much greater uncertainty regarding the values for these biological effect distributions in the individual patient and the particular tissue than will obtain for the statement of the physical dose. Nonetheless, the display of the estimated biological effect distribution should be an aid in the evaluation of the several treatment plans. At a minimum, this additional biological information regarding the plan options could provide warning signals when a particular plan might be predicted to yield an unanticipated probability of morbidity despite an attractive physical dose distribution.

The selected optimized plan will be employed in the simulation, which will primarily serve to document that the clinical placement of the beams covers the volume intended in the plan. If the plan is found to be practical, this will be indicated to the computer, which in turn will issue instructions to the treatment unit for gantry position, collimator angle, setting(s) of the multileaf collimator system, intensity modulation, patient support assembly positions, and preparation of patient records. Thus, treatment planning in the year 2000 will be quite different from and superior to that now considered to be standard medical center quality.

**Confirmation that the target is in the beam**

Employment of the most elegant treatment plan—a projected treatment volume-to-target-volume ratio of approximately 1.05—is of little merit unless there are means for confirming that all of the target is in the beam throughout each individual treatment session. Developments in this area fall into four classes: (1) portal visualization systems, either “beam’s-eye” or off-beam line techniques; (2) physician-introduced fiducial markers; (3) increased security of patient immobilization systems; and (4) methods for gating the irradiation with patient/anatomic part movement during the individual treatment.
On-line portal viewing system

Portal viewing systems (PVSs) are currently being introduced to the market by virtually all of the linear accelerator suppliers. The goal of a PVS is to provide the ready capability of confirming that the beam is covering the structures intended and, if not, to permit an easy—or, even better, an automatic—correction. However, available PVSs are still developmental and possess too little contrast to be of great practical merit for sites other than the head, neck, and, in certain cases, the thorax. The technical characteristics will undoubtedly evolve rapidly toward providing superior contrast and result in a clinically essential tool. Some researchers are considering developing systems that include a diagnostic radiographic unit in the treatment head to produce diagnostic quality in portal imaging. High-quality PVS could be a major advantage for treatment of lesions, which move appreciably between treatments and even during treatment. An important feature to be developed is that of digitization of the fiducial markers on the initial image, with a subsequent control system to turn the beam off if the fiducial markers move beyond a permitted range. Thus, continuous visual monitoring, which is labor intensive and error prone, would no longer be required.

Physician-introduced fiducial markers

Discrete anatomical features—edges of high contrast parts—are the fiducial markers used in current clinical practice for assessment of portal films. This is often quite difficult, as the markers are not well visualized, and only rarely is an anatomic marker properly seen on two beam paths. This means that determination of the position of the target in relation to the beam is often quite difficult or unsatisfactory. The future should bring about a much expanded use of a variety of physician-introduced fiducial markers of a high atomic number (Z) material, and hence, comparatively easy for visualization on portal films and or in the PVS.

Our experience in this area has been quite positive in the treatment of patients with intracranial, skull base, and paranasal sinus tumors. This has been based upon a technique which places two gold screws in the outer table on one side of the cranium and a single screw on the opposite side. This is done prior to the treatment-planning CT scan. The position of the screws relative to the target and any sensitive structures of interest is defined and included in the data used in the 3-D treatment planning procedure. At treatment, with the patient in the immobilization device, a pair of orthogonal films are taken. The centers of the screws on each of the films are digitized, and, thus, the relative positions of the screws one to the others are defined. By a software routine, the patient support assembly is instructed to move to the correct position, and a repeat set of films is then evaluated. With few exceptions, the target has been placed correctly in relation to the beam (± 1 millimeter [mm]). Markers are frequently employed to aid in simulation of patients with tumors of selected sites in the head and neck region, pelvis, and other areas. Our judgment is that there can be substantial reductions in treatment volumes by more frequent utilization of such a simple technical maneuver as insertion of several markers.

Patient immobilization systems

The developments in this field have been significant. Of special note have been devices for immobilizing the head for the treatment of intracranial and other head and neck sites. The repositioning of the head for fractionated treatment is now accurate to 1 mm. Thus, highly accurate beam localization of intracranial targets does not require the use of head frames, which are screwed into the cranium, or treatment by a single large dose. Target position definition in a space at most 1 mm is not feasible by use of even the highest resolution CT imaging techniques due to scan thickness, scan intervals, errors in marking target margins on the
CT/MR image, and variation between observers as to the concept of the target. The dose fractionation protocol will increasingly be based upon the radiation biological features of the tumor/normal tissue situation and not on the technical requirements for accuracy of immobilization.

Systems are now being developed and marketed for greater security and comfort in patient immobilization for most anatomic regions. The future is certain to see extended utilization of such systems and their improved derivatives regularly in definitive radiation treatments.

**Gating of radiation treatment to patient/anatomic part movement**

Structures in the thoracic and abdominal cavities move regularly with respiration and the heart beat. For radiation treatment in those sites based upon close margins, oncologists will have to employ techniques for gating treatment to such movements. There is no fundamental difficulty in devising the means for achieving progress in this area; only time, effort, and resources need be applied. Recent reviews of these technical developments include the November 1993 issue of Radiology and Oncology and Meyer and Purdy's *Frontiers of Radiation Oncology* (1995). 4

**CHANGES IN CLINICAL PRACTICE PATTERNS**

**Multi-modality treatment strategies**

Over the recent three decades, utilization of radiation as a sole modality has decreased sharply. This trend is likely to continue as (1) chemotherapeutic agents and multi-drug protocols are shown to yield clinical gains in terms of higher distant metastasis-free survival and local control probability; (2) conservative surgery is replaced with radiation and or chemotherapy; and (3) new strategies involving biological response modifier and gene therapy are shown to yield clinical benefits. At present chemotherapy is combined with radiation alone or with surgery in the management of a high proportion of patients with breast, esophageal, colorectal, anus, pancreas, bladder, high-grade glioma, pediatric tumors (Ewing's rhabdomyosarcoma, CNS, and the like), small cell lung cancer, lymphomas, and others. For many of these tumor types, the impact of the combined modality approach has been to augment both the rate of local control and metastasis-free survival. These results constitute one of the most important gains for patients whose treatment includes radiation. Further, quality of life has been greatly improved by replacing radical surgery with conservative surgery and radiation in cases of breast, head and neck, and rectal cancers and of sarcoma of soft tissues. Clinical studies of combined modality management will expand and provide further gains for patients.

**Widespread subspecialization within radiation oncology**

Specialization has been a characteristic of the development of the practice of medicine. There appears to be not only a continuation but an acceleration of this process in virtually all medical specialties. The present evidence is that there will be some shift toward greater numbers of young doctors entering primary care rather than a specialty practice. However, the individual physician to whom responsibility is given for management of the patient with a major medical problem is likely to be even more specialized. This is a simple reflection of the growth of knowledge and of a growing literature in each facet of medicine. Changes in the general field of radiology serve as striking evidence for this trend over the past forty years of extensive subspecialization. Consider that, in major academic centers, diagnostic radiologists concentrate in one specific anatomic region or imaging technique—thoracic, breast, neuroradiology, gastrointestinal, genitourinary, skeletal, CT, MR, etc. General diagnostic radiologists are rarities or have become extinct in large
medical centers. Radiation oncology has moved from being a subspeciality to a separate specialty.

The continuation of this process to subspecialization within radiation oncology is the natural consequence of the extraordinarily rapid expansion of our knowledge and experience bases. This includes for each type of tumor: the natural history, responses to various therapies administered alone or in combination, frequencies and severity of morbidities, tumor and normal tissue biology, radiobiology, epidemiology, efficacy of rehabilitation procedures, psychological components of patient care, basic and clinical genetics, cost of management, and many other factors. These advances have meant a virtual torrent of medical and scientific journal articles, monographs, books, symposia proceedings, and various governmental and nongovernmental reports. Patients expect their physicians to be knowledgeable regarding this rapidly accumulating information base as it pertains to his or her disease. These papers and publications are emanating not only from this country but increasingly from countries across the globe. For example, in 1992 alone there were 7,200 papers published on cancers of the lung, 5,200 on cancers of the breast, 1,800 on cancers of the rectum, and 1,800 on cancers of the bladder. Clearly, to be even moderately well informed about the activities in oncology related to a single tumor type requires a most serious effort. To be a generalist and also well informed is no longer feasible. The new "generalist" will have to limit practice to a relatively small number of tumor types.

If this seems a strong statement, consider how the practice of the general surgeon has changed during the past seven to eight decades; orthopedics, urologic, gynecologic, thoracic, plastic, and ear, nose, and throat procedures are infrequently done by a general surgeon today. Our patients will expect that we be more than technicians implementing treatments decided upon by surgical or medical oncologists. This obviously requires an intensive effort today and will be even more of a challenge with time.

Oncologic practice in large centers is rapidly evolving toward the use of different site/tumor specific teams, each of which is comprised of subspecialist representatives from radiation oncology, medical oncology, surgical oncology, pathology, diagnostic radiology, and nursing. In addition, there is often participation by basic scientists with interests in the specific tumor of concern. This means that for the major cancer treatment centers, there are now radiation oncologists whose practice is limited to patients with tumors at specific sites (such as head and neck, breast, central nervous system, gastrointestinal, genitourinary, gynecologic, thoracic), or to patients with specific histologies (lymphoma, sarcoma), or to patients of a specific age (pediatric oncology). Each of these have its counterpart in medical and surgical oncology as well as in pathology and radiology. Further, in radiation oncology, the physics group is also subspecializing, often working principally in stereotactic radiation techniques, intra-operative electron beam radiation therapy, or stereotactic brachytherapy. Additionally, some physicists work exclusively with one or a few of the site-specific teams. This trend is being seen also with radiation therapists, as patients with tumors in a given site tend to be treated on a single machine. The operation of such site/tumor specific centers in the larger hospitals clearly brings a higher level of experience and expertise into actual clinical practice for the diverse tumors and anatomic sites than is feasible for an individual attempting to cover the broad spectrum of patient problems.

This view implies that the present status of medical and radiation oncology as a single specialty in many countries will not persist. This is in part due to the fact that present chemotherapy drug and dose schedules are quite toxic and will probably become more so. Intensive use of present protocols requires a much more serious time commitment than is feasible for a clinician who is also involved in performing complex, high-technology radiation treatments.

Patients and their referring physi-
cians will be increasingly likely to insist that their care be planned and administered by a multidisciplinary team which makes a special concentration of study and practice on their particular tumor. This trend is likely to be accelerated by the broad coverage of medical matters in the popular press and television programs, where the activities of the multidisciplinary centers are presented in favorable terms. That such teams could provide advantages in quality of care is likely to be readily accepted by the public.

There are, however, counterpressures to this trend toward subspecialization, particularly in the establishment of small community radiation facilities by entrepreneurial firms. These will attract many patients to the generalist who works either alone or with one or two associates. Further, if the health maintenance organizations (HMOs) and other health care organizations can negotiate lower prices with these smaller facilities, the tendency will be to encourage patients to be treated there. How the balance will be established between the large subspecialized centers and the small community-based unit will be under continuous discussion and review for the foreseeable future. With reference to potentially fatal diseases, this writer predicts that public pressures will ultimately result in substantial concentrations of experience and resources to maximize outcomes. For this to be realized, physicians should seek out opportunities to describe to the public the predicted benefits from patient management by subspecialty teams as well as from the clinical use of new technologies, predictors, and combined modality treatment methods.

Facility utilization

The staffing, technical equipment, and general facility requirements for a major treatment center providing multi-disciplinary care will become progressively more stringent and more costly. With reference to radiation oncology, at a minimum they will need: linear accelerators fitted with computer-controlled multileaf collimator (MLC) systems; portal imaging systems; 3-D treatment planning systems with optimization software; record and verification systems; simulators integrated with treatment planning systems and linear accelerators; and easily applied stereotactic techniques for external beam radiation therapy or brachytherapy. Requirements for cost-effective utilization of such facilities will likely mean operation for more than the current eight-hour day and five days a week. There should be no surprise to see these complex and costly facilities operating on a twelve- to sixteen-hour day and/or a six- or seven-day week. These extended operations are already commonplace for some MR imaging centers. This is not likely to be constrained by staffing shortages, as there appears to be rapidly increasing numbers of radiation oncologists, physicists, and other trained personnel.

Larger practice groupings

The move toward radiation oncology practice based upon tumor-type specific teams and supported by an associated spectrum of technical capabilities will mean larger and larger practice groups. Further, for purposes of cost efficiency, we may expect integration into multi-institutional groupings. Mergers and integration of medical services are commonplace and will almost certainly become more so. Easy referrals within such systems will make more likely the cost-effective utilization of specialized and expensive facilities.

A growing proportion of radiation oncologists will be working in managed care systems and to some extent on a capitation basis. This will mean that the choice of medical procedure will be determined not only by the individual physician but will be affected by the policies of the HMO.

Special Treatment Facilities

In addition to the growth of centers with highly focused teams for the management of patients with tumors at spe-
cific sites, a small number of cancer centers with highly specialized technical facilities will be established to serve as regional, national, and even international resources.

**Fast neutrons**

Fast neutron beams are under continuing clinical evaluation in the United States, Europe, Japan, and South Africa. The published results for clinical trials and practice since the late 1990s do not clearly demonstrate clinical gains over photon therapy, with the probable exception of treatment of locally advanced carcinomas of the parotid salivary glands. Data from treatment of soft tissue sarcoma and carcinoma of the prostate are of interest and will be pursued but are not accepted as demonstrating superior results for neutrons. Therapeutic gain factors determined for fractionated (F-15) fast neutron irradiation of three spontaneous tumors systems of a C3H mouse (a mammary carcinoma, a fibrosarcoma, a squamous cell carcinoma) were not above 1, a disappointing result.

The active fast neutron therapy centers in the United States are at the University of Washington, Seattle; Harper Hospital, Detroit; Fermi Laboratory, Chicago; and the Cleveland Clinic, Cleveland. Several fast neutron facilities in the United States have discontinued activities, including MANTA, Washington, D.C.; University of California–Los Angeles; and the M.D. Anderson Hospital in Houston. New fast neutron facilities are to be constructed in Germany and Sweden. There is clearly needed in the relatively short term a definitive evaluation of the clinical efficacy (tumor control probability vs. treatment related morbidity) of fast neutrons relative to photons for those tumor and anatomic sites where the dose distribution for fast neutrons is approximately equivalent to that for photons. This would be valuable in assessing the potential of high linear energy transfer (LET) radiations in general as well as the emphasis to be placed on heavy ion beams.

There is one important difference in treatment protocols used in fast neutron treatments: essentially all treatments have employed overall times of three to four weeks. There might be a component of any observed gain due to the accelerated treatment rather than due to the radiobiological characteristics of the high-LET radiations. This needs to be considered in protocol designs used in the testing of the high-Z particle beam. A concern with the clinical application of high-LET beams is the apparently greater relative biological effectiveness for late damage, including radiation-induced tumors. Thus, the comparison of local control results at equivalent frequencies and severities of treatment related morbidity will demand observation over a prolonged time period.

**Heavy Particle High-LET Radiations**

The expectation for the high-Z particle beams—carbon, neon, argon—is that any gains relative to proton beams should be approximately comparable to gains of fast neutrons relative to photons, namely, similar dose distributions but quite different radiation biological characteristics.

The largest and most costly of these specialized radiation facilities is the HIMAC unit of the National Institute of Radiological Sciences in Chiba, Japan. This facility is unique in that it has been designed primarily for medical purposes. Thus, the physicians should have optimal access to the unit and not be in competition with nuclear physics research programs for beam time. HIMAC commenced patient treatments in 1994. In addition, there are plans for access by clinicians to the high-Z beams at the nuclear research facilities located at Darmstadt and at Julich (near Düsseldorf). Small numbers of patients are being treated at the nuclear research facility at Dubna, near Moscow. Serious discussions are in progress regarding the feasibility of the establishment of a heavy particle therapy facility near Milan. These several programs constitute a most special test-
ing of exotic particle beams in radiation oncology. This line of clinical research is not expected to have direct participation by an American facility in the near future. Earlier, Castro and colleagues had studied similar beams and acquired a major experience at the Bevalac at the University of California at Berkeley. They judged that the results provided promise for the application of heavy ion beams.

Proton Treatment Facilities

Proton beams constitute an extremely attractive means for reducing treatment volumes. This is due to the physical characteristics of proton beams: (1) finite range, (2) energy-dependent range, (3) range dependent upon the density of the tissue along each particle path for a proton of a given energy, (4) dose deep to the end of range is zero, and (5) for a modulated energy beam the surface dose is in the range of 70 to 100 percent depending on the depth of the target from the surface, that is, less attractive than for the photon beams. However, regarding this last point, when multiple fields are utilized for deep lesions, this is not a factor of clinical significance.

The critical feature is that for each beam path there is no proton dose deep to the target. In comparing proton beams with 3-D conformal photon therapy, proton techniques can utilize as many beams (static or mobile), intensity modulations, etc., as a photon technique. Thus, the laws of physics demonstrate that integral dose will always be less for proton than for photon treatment.

To the extent that the smaller treatment volumes permit the employment of higher doses to the target, there would be anticipated increments in tumor control probability. The actual clinical experience in the use of proton beams in the treatment of cancer patients is based mainly on treatment of patients with uveal melanoma and skull base chondrosarcoma and chordoma. For those lesions there have been impressive five-year actuarial local control rates of 95 percent, 97 percent, and 59 percent, respectively.11 These results are interpreted as constituting gains over those obtained by photon techniques. Other sites under current clinical trial include parametral sinus, nasopharynx, pharyngeal wall, prostate, high-grade glioma, arteriovenous malformations, meningioma, acoustic neuromas of the spine and sacral sarcomas, retinoblastoma, and acoustic neuromas. By far the greatest number of patients treated with proton beams have been treated for benign intracranial lesions. The total world experience with proton therapy is some thirteen thousand patients.12 Of this total, nearly 75 percent have been treated for benign intracranial lesions, uveal melanoma, and skull base/spine sarcomas.13 Accordingly, data from proton treatment of the more common malignan neoplasms have accumulated.

Currently there are plans for about twelve new proton beam radiation therapy centers throughout the world.14 Many of these are projected to be designed and built for radiation treatment and not as physics research facilities with a medical annex. At present the only facility built exclusively for medical purposes is that at Loma Linda University in California. The second one is the facility under construction at the Massachusetts General Hospital. It is to be hoped that there will be collaboration between centers as they are brought into clinical operation so that data may be rapidly generated for a number of important disease sites. A start in this direction has been the formation of the Proton Therapy Oncology Group (PROG) by the National Cancer Institute and the American College of Radiology. Their intent is to facilitate collaboration between various proton beam centers within the United States and abroad.

Intraoperative Electron Beam Therapy

Intraoperative electron beam therapy (ORT), combined with external beam radiation and resection, is clinically advantageous in the treatment of
patients with locally advanced rectal carcinoma and retroperitoneal sarcoma, the advantages being an increment in survival and local control relative to that obtained by external beam radiation and surgery. There appears to have been a modest gain in survival time of patients with carcinoma of the pancreas but not in long-term survival rate. With respect to facility design and use, there is movement to have linear accelerators installed in operating room suites. This contrasts with the cumbersome and costly procedure of transferring the patient under full anesthesia from the operating room into a prepared treatment room in the radiation oncology department or dedicating the treatment room for the entire day of the IORT procedure. Such special facilities should increase the ability to test IORT against a greater spectrum of tumor types and sites.

**High Technology Brachytherapy**

The advantages of brachytherapy are well recognized and yield minimal treatment volumes in well-performed implantations. For complex anatomic situations, brachytherapy is being performed by stereotactic techniques (especially for intracranial lesions) and by CR or ultrasound for other sites. Preliminary studies are in progress at the Brigham and Women’s Hospital using online MR imaging to facilitate high-precision implantation. The applications of these methods are allowing an expansion of brachytherapy and should result in some improved results.

**Boron Neutron Capture Therapy**

This strategy, initially proposed by Locher in 1932, has had long and serious appeal. The principal interest among clinicians involved in the boron neutron capture therapy (BNCT) programs is high-grade glioma. This is based largely upon the fact that these tumors almost exclusively are local problems; nearly all patients succumb to the local growth and complications of treatment. Secondly, there is the expectation of a greater concentration differential of the boron-containing compound between tumor and normal tissue. Early work on these tumors was not successful and has been interpreted as the result of poor differential concentrations of boron. New compounds are now being investigated. There are active clinical therapy programs at Tokyo for gliomas and cutaneous lesions. New programs are being developed at Tufts/ Massachusetts Institute of Technology (MIT), Boston; Brookhaven National Laboratory (BNL)/Stony Brook, Long Island; Petten, the Netherlands; Sydney University, Australia; Ohio State University; and Idaho National Engineering Laboratory. Three facilities have the epithermal beams most desired for BNCT of deeply-sited lesions: Tufts/MIT, BNL, and Petten.

**Radiolabeled Antibodies and Metabolites**

This is a field of high potential and certainly sustained interest due to the very attractive rationale: incorporation of a radioactive atom into a cancer-specific compound, such as an antibody, metabolite, or antisense oligonucleotide, that is selectively concentrated in tumor tissue. Some worthwhile achievements have been realized in the use of this approach for diagnostic imaging. Research in this field for treatment of solid tumors has yielded obvious clinical gains. Nonetheless, my expectation is that intensive research into tumor biology will yield molecules able to accumulate highly selectively in tumors. Then radiolabeling should not be beyond the capabilities of pharmacologists and will result in a new modality. This category of treatment may not require highly specialized facilities but instead would need a specialized staff.

**Individualized Prediction of Patient Response to Radiation**

Currently, clinicians utilize a substantial number of useful response indicators in regular practice. These are: tumor size, histological type, histologi-
cal grade, anatomic site, hemoglobin, sex, age, clinical presentation (exophytic vs. infiltrative), presence of certain genetic diseases (for example, ataxia telangiectasia), and presence of active autoimmune disease. In addition, there are physical factors; chief among these are dose per fraction, time between fractions, and total dose. LET is also a parameter of response. Thus, an experienced clinician can provide quite useful estimates of the likelihood of local control and of clinically important treatment-related morbidity following a specified treatment protocol in the individual patient. Even so, some uncertainty remains for the specific patient.

There are several additional potential predictors of response of tissues to radiation under active clinical and laboratory evaluation. The potential for success in the research for new predictors will be limited by: (1) the accuracy with which the value of the new test parameter may be determined, (2) the relationship between the value of the parameter and local outcome, and (3) heterogeneity with respect to this new parameter among tumors accessed into the study.

Were the predictive power to be high, there would be a potential of identifying tumors of a specified type, size, site, etc., for which the standard treatment would be predicted to fail in an unacceptably high proportion of patients. The value for the new predictors might indicate the use of an alternate treatment method for an expected gain.

Inter tumoral heterogeneity is the principal determinant of the slope of the dose response curve. Consider these simple calculations. Cell kill follows Poisson statistics. For a population of tumors each of which contains about $10^8$ identical clonogens, the slope of the dose response curve for tumor inactivation would correspond to a $\gamma_{50}$ of about 7. However, the slope of an actual population of clinical tumors is not likely to be greater than 2; the difference being the consequence of intertumoral heterogeneity with respect to one or more of the determinants of response. This difference between $\gamma_{50}$ of 7 and 2 is the basis for anticipation of clinical gains from efforts to develop new physiological and radiation biological predictors. By critical assessment of the values obtained from measurements of one or more of the new predictors, there is a potential for devising an improved treatment strategy for the individual patient.

For optimal design of a clinical trial of a procedure which modifies a particular response, the eligibility requirement for accession into the trial must include evidence that the tumor (patient) is expected to benefit from that procedure. For example, a trial of a method which improves tissue $pO_2$ but accesses tumors that do and do not have hypoxic regions would have little prospect of demonstrating a gain even though a substantial gain would be obtained when applied only to tumors with hypoxic regions.

Current investigations of response predictors are directed principally toward three general lines of research: (1) determination of cellular radiation sensitivity of the tumor or normal tissue; (2) characterization of the tumor in physiological and biochemical terms; (3) definition of the proliferation kinetics of the tumor and normal tissue cells. Additional predictors being investigated include genetic assessment of the factors that determine DNA damage repair, predispose the development of distant metastases, and indicate sensitivity to radiation and chemotherapeutic agents.

Inherent radiation sensitivity is being measured in vitro on freshly derived cell lines for determination of SF$_2$, MID, $D_\alpha$, $\alpha$, $\beta$, and $\alpha/\beta$ of cells in exponential or plateau growth phases, using colony formation as the endpoint for cell viability. The results of the various published studies have been mixed. There is one strongly positive result: the Courtney Mills assay on fresh cells from carcinoma of the uterine cervix studied at Manchester. For $SF_2$ values <0.4 and >0.4 there was a wide separation between actuarial local control and local failure rates. These various $SF_2$ assay techniques are char-
characterized by large coefficients of variation, around 40 percent.\textsuperscript{23} This means that the absolute SF$_2$ as measured on an individual patient is of uncertain value. Further, there is no close correlation in SF$_2$ values determined on the same cell lines in different laboratories or for different assay techniques.\textsuperscript{24} These factors mean real uncertainty, at this writing, as to the value of available assay methods in determining cellular radiation sensitivity \textit{in vitro}.

Radiation sensitivity of tumor cells as they live in tumor tissue is, of course, the property of interest rather than the sensitivity of cells \textit{in vitro} under near optimal metabolic conditions. The principal end-points for estimation of cell sensitivity \textit{in vivo} under current investigations include micronuclei formation, comet assay, and the frequency of specific chromosome breakage, etc. There are at this writing no data that establish any of these techniques as a valid predictor. Experimental error inherent in these methods is not likely to be less than that for cell survival \textit{in vitro}. Quite encouraging results have been published which indicate that the severe response of normal tissue to radiation correlates with the sensitivity of the cells of that normal tissue when assayed \textit{in vitro}.\textsuperscript{25} Bentzen and colleagues have discussed the choice of end-points of normal tissue response and the \textit{in vitro} assay.\textsuperscript{26}

As pO$_2$ is a proven powerful determinant of cell lethal response to radiation and hypoxic regions have been demonstrated in many human tumors, the measurements of pO$_2$ in the individual tumor are a subject of much clinical research. Each of three reports of measured pO$_2$ before radiation treatment has shown a strong predictive power for local control.\textsuperscript{27} Further, tissue pO$_2$ can be manipulated for potential therapeutic advantage. Hence, the intense interest in the role of tumor pO$_2$ in determination of treatment outcome.

The electrode technique is the only one that measures pO$_2$ directly. Limitations of this method include applicability only to accessible tumors, its invasive nature, and uncertainties of measured pO$_2$ values, especially at ≤5 mm mercury. Electrode measurements of pO$_2$ in human tumors are being performed for carcinomas of the oral cavity, uterine cervix, skin, anus, and metastatic nodes in the cervical regions. There are indirect methodological corrections which could be utilized for deep-sited tumors.\textsuperscript{28} The accuracy of such techniques is not well defined at this time. Among the indirect procedures expected to provide evidence in patients of the presence of hypoxia are tissue blood flow, binding of certain molecules (for example, misorindazole), comet assay, and MR spectroscopy.\textsuperscript{29}

Presently, there is a need to define the ability of measured pO$_2$ values to predict outcomes on a much larger database than those of published results to date. When and if this is achieved, the efforts should be pushed to devise other means for assessing tissue pO$_2$ so that deep-sited tumors can also be investigated.

Proliferation kinetics of tumor clonogens during a course of fractionated dose irradiation increase the number of clonogens to be inactivated and, hence, reduce tumor control probability. Thus, for rapidly dividing tumor cell populations, treatment might be more effective when administered on an accelerated schedule, for example, two or three fractions per day. Currently, RTOG is sponsoring a four-arm trial of accelerated fractionation irradiation against head and neck cancer: a control treatment of 2 gray (Gy) once per day to 70 Gy and three different accelerated methods (RTOG protocol 90-03). The most extreme test of accelerated dose fractionation is the CHART trial at Mt. Vernon Hospital, which features radiation administered in three fractions per day for twelve days; this is compared with conventional fractionation.\textsuperscript{30} For this category of trials, the measurement of the proliferative activity of each tumor is made. There are means available, such as potential doubling time (T$_D$), for these measurements.\textsuperscript{31}

Results of a European Organization for Research and Treatment of Cancer (EORTC) trial (protocol 22851) indi-
cate that tumors with short $T_{\text{pot}}$ values (rapid proliferation) treated by conventional dose fractionation did less well than those with long $T_{\text{pot}}$ values.\textsuperscript{32} For tumors with long $T_{\text{pot}}$ values, those greater than 4.5 days, results were the same for treatment by the accelerated or conventional dose fractionation. Additional studies are in progress on this question in several centers and interinstitutional groups. These should provide improved estimates of the merit of shortening overall times of treatment. Further methods are needed to estimate clonogen division rate during treatment.

Withers and group have analyzed a very large body of clinical local control data and concluded that the dose to achieve a specified local control probability was independent of time up to three to four weeks; after that point, the dose for that response increased at some 0.6 Gy/day.\textsuperscript{33} This gives additional emphasis to the attention which needs to be paid to overall treatment times.

An alternate approach is to employ biological techniques which suppress cell proliferation. Studies are in progress in the laboratory on biologicals which might achieve a blockage of cell division over the relatively brief period of treatment.

For trials of both $pO_2$ and cell proliferation kinetics modification, there is uncertainty as to the adequacy of measurements made only prior to the commencement of treatment. Should similar determinations be performed at one or even more points during the course of fractionated dose irradiation?

**LONG STANDING QUESTIONS—FUTURE ANSWERS?**

There are a number of questions which have vexed radiation oncologists for many years that are likely to be answered definitively within the next two to three decades. This effort will be aided greatly by the design of trials with eligibility requirements limiting access to tumors with appropriate biological characteristics (see above).

Since the early 1950s radiation oncologists and radiation biologists have been studying the role of hypoxia in tumors as an important causative factor of local failure.\textsuperscript{34} Strategies that have been investigated to minimize the importance of hypoxia include respiration of oxygen or carbogen at normal pressure, oxygen at increased pressure, intraarterial $H_2O_2$; administration of hypoxic cell sensitizers (such as misonidazole), agents specifically toxic to hypoxic cells; erythropoietin prior to the commencement of radiation to bring hemoglobin up to normal levels, and high-LET radiations and radiation therapy under conditions of local tissue hypoxia (tourniquet technique for extremity sarcomas). Despite the lack of clear successes, extensive laboratory research has continued unabated. The availability of reasonably reliable methods for measuring $pO_2$ in accessible human tumors is stimulating renewed interest in attempts to modify tumor tissue $pO_2$ distributions. Results of well-designed trials are expected to provide an evaluation of the importance of hypoxic tumor cells to outcome in radiation treatments. A current series of trials is based upon the work of the Gray Laboratory.\textsuperscript{35} These feature respiration of carbogen at one atmosphere pressure to reduce diffusion limited hypoxia and administration of nicotinamide to reduce perfusion limited hypoxia, and these are integrated with an accelerated treatment protocol to decrease the importance of cell proliferation.

Due to the very active clinical trial programs in many parts of the world of accelerated dose fractionation, the clinical gain for each of several tumor types and for specific cell proliferation kinetics profiles should be firmly defined within one to two decades. In parallel with these endeavors, the benefit of administration of radiation in quite small doses per fraction—at less than 1.4 Gy—is also expected to become known.

The clinical efficacy of high-LET radiations in clinical radiation oncology should be well established in the future. This will come about from analyses of
outcome data from closed Phase III trials and ongoing trials of fast neutron therapy. To a lesser extent there will be data from the testing of high-Z particle beam therapy. In addition, the predictive power of measured values of cellular radiation sensitivity in vitro and even in vivo will be defined.

Included here should be the characterization of the immunological status of the patient and the immunogenetic relationship between the patient and the tumor. There will surely be developed new and more effective methods for altering specific components of the immunological status of the patient, so as to augment the efficacy of the anti-tumor reaction.

This work on the immune reaction has important possibilities for enhancing the diagnostic accuracy of radioisotope labeled antibodies. This may well extend to therapeutic success for a few selected tumors, for which there is great specificity of the antibody to the tumor associated antigen, a large number of receptors/tumor cell, and good access of the antibody to the tumor cell and, hence, the antigen. This is an area which has been the subject of substantial attention in experimental animal tumor systems but has seen modest success when studying spontaneous autochthonous tumors. The level of research in tumor immunology gives good prospects for some gains in either diagnosis or treatment of the cancer patient.

INCREASED AWARENESS OF THE LATE SEQUELAE OF RADIATION TREATMENT

There will be a much heightened sensitivity to and awareness of the late changes following radiation treatments as large numbers of patients will be surviving twenty to forty years postradiation. This concern will result in many studies that will contribute to the understanding of the role of dose, anatomic part irradiated, treatment volume, patient age, use of chemotherapy concomitantly or at separate times, and observation time. With reference to radiation-induced tumors, there will almost certainly be an increase (probably of a nontrivial magnitude) over the currently recognized frequency of 0.5 percent at twenty years after treatment with radiation alone in adult patients and significantly higher for patients treated by radiation and chemotherapy. This will place much greater pressure to use treatment techniques which involve the irradiation of smaller volumes of nontarget tissues. Radiation-induced morbidity does not develop in unirradiated tissues, and society is likely to be decreasingly tolerant of morbidity developing in nontarget tissues. This is significant, as most of the major treatment related morbidities arise in nontarget tissues.

STANDARDIZATION OF RADIATION ONCOLOGY PRACTICE

The trend toward the use of accepted or standard treatment techniques is expected to be strengthened with the continued publication of “good” results from large series. By this, I mean that for the more common tumors there can be expected to be a generally accepted radiation treatment technique and dose (dose per fraction, total dose, and overall time). Treatment by other than an approved method will be less easy and surely more risky than at present, given the exigencies of both litigation and managed care. The exception will be limited to evaluation of new strategies on institutional and or governmental-authorized protocols.

RADIATION ONCOLOGY EDUCATION AND MANPOWER

The available data indicate a substantial surplus of radiation oncologists within the next decade. D. Flynn estimates that there is a net increase in radiation oncologists in the United States of 120 per year (160 graduates less 35 retirements and 5 deaths among active practitioners). This would mean some 1,200 additional radiation oncologists by 2003. The impact would be a reduction in the number of new patients per year per full time equiva-
lent to only 172 by 2003. This would be down from 194 in 1993 and 212 for the period 1974 to 1990. These estimates make no allowance for a probable decrease in the number of patients being referred to radiation oncology. Currently, some 48 percent of cancer patients receive radiation. Further, the health care system can be expected to specify that each clinician be responsible for more rather than fewer patients. However, definitive treatments will require more physician time as the more sophisticated techniques come into clinical use. These figures, then, stress the urgency to assess critically the large number of young doctors being trained in this specialty.

There is an obligation to enhance the quality of education of young doctors accepted into our residency programs. Education of residents in radiation oncology will be modified and, it is hoped, enhanced by the introduction of many computer-aided teaching tools. For example, teaching of human anatomy should be much improved by the 3-D visualization of any anatomic part or region from all angles, external and internal. Perhaps virtual reality, holograms, and other methods will become available and, if so, should be real boons. Interactive teaching programs should aid in all aspects of didactic teaching. Further, one can expect there to be simulations of all of the procedures in radiation oncology. These same capabilities will also become available in all facets of medical practice, facilitating and accelerating the learning and retention processes. Surely these projected tools will make for better informed and more continuously up-to-date physicians.

Through regulation of payment for radiation oncology services, the number and the distribution of radiation oncologists and radiation oncology facilities will be controlled to meet the expected needs of the American population. There will probably be pressure in the United States for the number of patients treated per radiation oncologist per year to go up toward the levels current in other countries.

**Radiation Oncology in Twenty to Thirty Years**

Despite the virtual certainty of large gains in the effectiveness of radiation oncology, a serious question is whether or not advances in basic genetics and the applications of genetics to clinical oncology will be so great that we have to consider whether radiation will even be needed as a major therapeutic modality within thirty to forty years. There are serious and highly respected scientists, in addition to the popular press, who are so optimistic about the potentials of the clinical applications of molecular biology and gene therapy to oncology that they have predicted that surgery, radiation, and chemotherapy as currently employed would be unnecessary. However, the number of years required for even partial realization of this remarkable goal is clearly uncertain. Lewis Thomas, one of the most highly regarded thinkers and spokespersons in medicine, stated in 1983 that "cancer would no longer be a problem by the year 2000." Achievement of this nirvanic state in oncology will require the resolution of a number of quite important problems within a very short time period. Regrettably, at this writing such a happy turn of events does not appear to be a serious prospect for the near or even for the not-so-near future. Popular weekly magazines such as *Time* and *Newsweek* detail glowing accounts of the changes to be wrought in oncology as a consequence of the research in molecular biology.

There can, however, be little doubt that there will be: (1) dramatic increments in the knowledge of the oncogenic process in molecular terms, (2) important gains from the utilization of that knowledge in diagnosis and prognostication, and (3) major advantages accrued from the capacity to identify individuals with high risk of development of a neoplasm, in many instances of a specific type. The practical clinical utilization of these genetic insights in the eradication of solid tumors is less clear.
Genetically defined diagnostic categories

The genetic analysis of the biopsy specimen from an established tumor should bring an extensive revision of diagnostic categories; the new pathological types will be based not only on morphological appearance and immunohistochemical profile but, importantly, upon a genetic characterization with special reference to genes which determine, among other things, the metastatic potential, capacity to repair radiation damage, ability to cope with cytotoxic chemicals, and rate of cell proliferation.

Already, this area of research has led to quite accurate predictions of the clinical course of neuroblastoma. Namely, the extent of amplification of the N-myc gene is inversely related to survival probability. The number of copies of N-myc is now, by a substantial margin, the most important diagnostic feature of neuroblastoma. There is every confidence that there will be developed highly reliable genetic indicators of the degree of malignancy for many tumors. Preliminary experience with genetic markers as prognostic markers for metastatic probability appears positive for carcinomas of the breast, ovary, and lung. This information will mean a sophisticated individualization of the management strategy.

Identification of individuals at high risk for development of specified tumors

A parallel series of developments will result in the capacity to identify individuals with the genetic alteration which will at some point be associated with the appearance of specific neoplasms. The consequence will be that these particular persons can be monitored carefully for the earliest evidence of that specific tumor and treatment implemented at a minimal stage. Alternatively, there may be "preemptive" therapy in identified patients. For example, at a specified age, bilateral mastectomy in women carrying defined genetic abnormalities associated with exceptionally high probabilities of developing breast cancer is being performed in a few clinics.

As the skill in defining the genetic characteristics that are regularly associated with development of particular neoplasms is expanded, the frequency with which patients are seen with more than minimal disease should plummet or at least decrease appreciably. This will, for some categories of tumors, mean that those patients will be managed by rather simple procedures and experience a higher cure rate. We need only consider the impact of the extensive use of the Pap smear on the frequency distribution of stages of carcinoma of the uterine cervix. In communities where this test is commonly employed, very large proportions of patients with carcinoma of the uterine cervix are treated by conization or hysterectomy for carcinoma in situ or early stage disease. Genetic study of the general population or of defined high risk individuals is likely to have a similar impact on at least some diseases. The result will be fewer patients requiring radiation therapy.

For many tumor categories, knowledge of a virtual certainty of a later development of tumor in an individual patient is not likely to provide an opportunity to diagnose the tumor at a sufficiently early stage to augment sharply the therapeutic outcome, at least from the use of currently available treatment methods. This limit might apply to, for example, carcinoma of the pancreas or high-grade glioma. As there is virtually no clinical experience with these tumors at very small size, up to 1 centimeter, we do not know the efficacy of even current treatment methods against such small lesions. There might be a pleasant surprise.

Gene therapy

As recent reviews demonstrate, the potential for use of genetic approaches in therapy has clearly attracted intense interest and excitement in biomedicine. The basic strategy is to define the genetic abnormality and to determine the gene construct which would reverse and eradicate the pathological process and then proceed to correct the genetic abnormality. This requires (1) the availability of needed gene(s), (2) an appropriate vector for the delivery of the new genetic material to some or all of the affected cells, (3) integration of the new
gene(s) into the genome of those cells and commencement of proper function in both quantitative and qualitative terms. (4) the new gene function be stable, and (5) little toxicity of the procedure and risk of secondary morbidity from the use of a viral or other vector relative to the clinical effect on the disease process being treated.

To date partial success in gene therapy has been realized in the treatment of a small number of patients whose diseases are due to defects in a single gene. This has apparently been accomplished with ADA (adenosine deaminase deficiency) and LDL receptor deficiency resulting in familial hypercholesterolemia. For these treatments the patients' target cells were transduced ex vivo and then reimplanted. These brilliant achievements bode well for advances to come. The major question is the effort and time required for these to be realized. The current issue of the influential London Economist gives the year 2015 as the time for success against the recessive single gene mutation diseases.11

For genetic treatment of this class of disease, there is no need to affect all cells of the particular category in the patient. The requirement is to have altered sufficient cells to produce a minimal quantity of the deficient compound, be it an enzyme, hormone, metabolite, etc. However, the transfected cells must function in a stable manner for very long times. This contrasts with the situation for anticancer treatment where all cells of the tumor must be altered genetically unless there is a significant bystander effect of the gene product. On the positive side is the fact that the action of the gene need persist only for the period required to inactivate the cell.

That success of gene therapy of even the single gene diseases is far from straightforward is evident in the fact that results to date are limited to only two such diseases, small numbers of patients, relatively short follow-up observation periods and a palliative result. This remains true despite the cloning of the altered gene some years ago. For example, the genetic defect for hemophilia was defined some years ago with no major clinical benefit to date. This indicates the difficulties in carrying detailed understanding of the gene alteration forward to make an effective clinical treatment strategy.

The clinical testing of these methodologies has just commenced. At present, much of the effort is and will continue for some undefined period toward overcoming the technical problems of transfecting appropriate numbers of target cells of the patient either using in vivo or ex vivo techniques.42 Extension of these strategies to treatment of the cancer patient is sure to prove more difficult. This is due to several factors: the genetic abnormality in the cancer cell is more than one gene alteration; there is extensive genetic heterogeneity of tumor cells; the delivery of the genetic material is complicated by the pathophysiology of tumor tissue, that is, poor to nearly absent perfusion of regions of tumor; and the new genetic material must be delivered to all or nearly all of the tumor cells. For some proposed mechanisms there would be an important bystander effect so that the cell kill would be greater than the actual number of transfected cells.

The inherent pathophysiological characteristics of solid tumors impose such severe constraints on the selective delivery of gene therapy agents to a useful proportion of tumor cells that the eradication of established tumors by such strategies does not appear to be a high likelihood in the near term. These factors are almost certain to prove a serious constraint on the efficacy of gene therapy against epithelial and mesenchymal tumors. However, were the gene therapy strategy to achieve a cell kill by methodologies which were to be relatively nontoxic of only 90 percent, this would not be insignificant. This is especially so if gene therapy could be repeated once or more times. Such a treatment could be combined with other modalities, say, radiation, to achieve eradication of all tumor clonogens at a cost of lower treatment-related morbidity than that following the use of radiation alone.

An alternate genetic approach is to introduce genes designed to make the
Gene activation by radiation

There is now convincing evidence that radiation doses of the magnitude employed clinically activate a variety of human genes. There is potential for the use of this category of response to therapeutic advantage. This effect is for many genes of small degree and the duration of the activation is rather short. Nonetheless, this phenomenon is of interest and is being pursued in the laboratory.

SUMMARY

From the perspective of this radiation oncologist, there is an impressive array of important advances in radiation oncology to be brought into clinical practice in the coming several decades. This is to be accompanied by a startling increase in the understanding of the biology of tumor initiation, progression, metastasis, and response to the diverse therapies employed and being developed. Within our specialty, the elegance of actual treatment will be advanced markedly. Further, we almost certainly will have the capability to predict the tumor and normal tissue response in the individual patient to a greater degree than now obtains. This will provide the basis for the design of treatment strategies which maximize the therapeutic efficacy of the treatment modalities available. Moreover, the questions which have occupied so large a portion of our intellect, time, energy, and resources will have been answered, and these capabilities will be directed to new problems. An important basis for a high and general level of optimism is the exceptional quality of new entrants into the century-old field of radiation oncology.

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5. BRS Colleague.
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