Alternative Radiation Modalities

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The early recognition that x-rays could produce local tumor control in some patients and not in others led to the notion that other forms of ionizing radiations might be superior.

Neutrons first were introduced in a speculative way, not based on any particular hypothesis. The later use of neutrons and the introduction of protons, negative π-mesons, and heavy ions all were based clearly on a putative advantage, either of physical dose distribution or radiobiologic properties.

The use of neutrons following World War II was based squarely on the premise that the presence of hypoxic cells limits the curability of human tumors by x-ray therapy, so that the lower oxygen enhancement ratio (OER) characteristic of neutrons might confer an advantage. An alternative rationale for neutrons, proposed at a later date, was that their relative biologic effectiveness (RBE) is larger for slow-growing tumors, so that they may have an advantage in a limited number of specific human tumors.

Protons have radiobiologic properties similar to x-rays, and their introduction into radiotherapy was based entirely on the superiority of the physical dose distribution possible with charged particles. Negative π-mesons and heavy ions were introduced with the hope of combining the radiobiologic advantages attributed to neutrons with the dose distribution advantage characteristic of protons.

Neutrons have been shown to be superior to x-rays in a limited number of situations, specifically for the treatment of prostastic cancer and salivary gland tumors. A number of controlled clinical trials have been performed for a wide variety of cancer sites, but a gain was apparent only in these few circumstances. Protons have found a small but important niche for the treatment of uveal melanoma and tumors such as chordomas that are located close to the spinal cord and therefore benefit greatly from the localized dose distribution. The wider use of protons for broad-beam radiotherapy is being tested, but no advantage has been proven yet. Negative π-mesons and heavy ions have been used to treat hundreds of patients, but prospective randomized trials have never been completed to prove their superiority over conventional x-rays. Their enormous cost would be justified only by a significant gain.

The casual reader may be content with this overview of alternative radiation modalities and may not wish to proceed further in this chapter. Interest in high linear energy transfer (LET) radiations for radiotherapy largely has waned, but protons are very much in vogue. In this chapter neutrons and protons are considered in turn.

Fast Neutrons

Rationale

Neutrons first were used for cancer therapy at the Lawrence Berkeley Laboratory in Cali-
California in the 1930s. Their use was not based on any biologic or physical rationale; they were used only because they represented a new modality that might be useful in hopeless cancer cases, for which conventional radia-
tions were known to be ineffective.

After World War II, interest in neutrons for cancer treatment was renewed at the Ham-
mersmith Hospital in London, as a result of studies that implied that tumors contain hypoxic cells and that cells deficient in oxygen are resistant to killing by x-rays. The rationale for neutrons at this stage, therefore, was their lower dependence on oxygen for cell killing, together with the premise that viable hypoxic cells limit curability by x-rays.

Clinical trials to date have shown clearly that neutrons do not offer an advantage over x-rays across the board for a broad spectrum of tumor types. Nevertheless, there is tantalizing evidence that they give better results for certain types of tumors. This, together with other evidence, has resulted in a rethinking of the role of hypoxic cells and the admission that they probably are not as important as previously thought, at least in multifraction regimens in which reoxygenation can be effective. The revised rationale for neutrons, therefore, is that RBE varies for different tumor types, being high for some that are slowly proliferating. On this basis neutrons would be expected to offer an advantage only in a few selected types of cases. The idea is that slowly growing, well-differentiated tumors may be analogous to the slowly proliferating tissues responsible for late effects, and it is well documented that neutron RBEs are higher for late than for early effects, at least for treatment schedules involving many fractions.

The rationale for the use of neutrons has undergone a considerable evolution over the years. The biologic properties of neutrons differ from those of x-rays in a number of respects, and it is not clear which is the most important in a clinical situation.

**Practical Sources**

The only practical source of neutrons for clinical radiotherapy is a cyclotron. A cy-
clotron is an electric device capable of accelerating positively charged particles, such as protons or deuterons, to an energy of millions of volts. The particle is accelerated by being made to pass repeatedly through an electric gradient while being held in a circular orbit by a magnetic field produced by a huge magn-
et. The path of the particle, as it accelerates, is a spiral, until it is extracted from the ma-
chine. The principle of the cyclotron was conceived by Ernest Lawrence at the University of California at Berkeley in 1931, when he realized that the time taken for a charged particle to complete a circular orbit in mag-
etic field was independent of the radius of the orbit.

Neutrons can be produced in a cyclotron by accelerating deuterons or protons and making them impinge on a beryllium target (Fig. 24.1). Using the \( d^+ \rightarrow Be \) process, a high yield of neutrons is readily achievable; the disadvantage is that the cyclotrons needed are relatively massive. Early on, a few low-energy machines, of 15 MeV or less, were built specially for medical use and installed in hospitals, with their time divided
between neutron cancer therapy and the production of short-lived positron-emitting radioisotopes. This was the policy in Great Britain, with neutron therapy being administered with small cyclotrons using the \( d^+ \rightarrow \text{Be} \) process at Hammersmith and Edinburgh. Unfortunately, the limited energy from this process results in poor percentage depth doses, and only relatively superficial tumors in the head and neck could be treated adequately. To obtain penetration comparable to megavoltage x-rays using neutrons produced by the \( d^+ \rightarrow \text{Be} \) process requires an accelerating energy of about 50 MeV, and that means a massive cyclotron, much too large to be accommodated in a hospital. In the United States several high-energy machines (22-50 MeV), initially designed and built at enormous cost for high-energy physics research, were modified and used to generate neutron beams for cancer therapy on a part-time basis.

More recently, cyclotrons to produce neutrons have been built using the \( p^+ \rightarrow \text{Be} \) reaction. Because a proton has half the mass of a deuteron, the cyclotron can be sufficiently small to be installed in a hospital, particularly in the case of cyclotrons based on superconducting technology.

Neutron spectra produced by the two processes are shown in Figure 24.2. If a beam of deuterons impinges on a beryllium target, the proton is stripped from the deuteron and carries with it some of the kinetic energy of the deuteron, a process illustrated in Figure 24.1. The neutron spectrum consists of a single peak, with a modal value about 40% of the energy of the incident deuterons. Thus, 50-MeV deuterons would produce a neutron beam with a modal energy of about 20 MeV. If accelerated protons impinge on a beryllium target, neutrons are produced by a knock-on process, and the neutron spectrum spans a wide range (Fig. 24.1). Many low-energy neutrons are produced, as well as neutrons up to energies close to the accelerating energy of the incident protons. In many cases it is necessary to use a filter of some hydrogenous material, such as polyethylene, to filter out preferentially some of the low-energy neutrons that would “spoil” the depth-dose curves because they are absorbed at superficial depths (Fig. 24.2). A 50-MeV proton cyclotron produces neutrons with depth doses similar to a deuteron cyclotron of the same or slightly higher energy and is a fraction of its size. Dedicated hospital-based cyclotrons in the 50- to 70-MeV range using the \( p^+ \rightarrow \text{Be} \) reaction are used in neutron cancer therapy in a number of countries. Such machines can be built with an isocentric mount and adjustable multileaf collimators. The resultant depth doses are comparable to a 6-MV x-ray Linac. Controlled clinical trials to compare neutrons with x-rays now can be performed without the neutrons being at a disadvantage because of poor physical characteristics.
Percentage Depth Doses for Neutron Beams

An essential factor in the choice of a neutron beam for clinical use is its ability to penetrate to a sufficient depth. Figure 24.3 is a comparison of the percentage depth doses for various photon beams with those for neutrons produced by cyclotrons using the $d^+ \rightarrow \text{Be}$ or $p^+ \rightarrow \text{Be}$ processes. The lower-energy Hammersmith cyclotron, used in the early trials, gave appreciably poorer depth-dose characteristics and is in fact comparable to a cesium-137 unit. The higher-energy cyclotrons show considerably better penetration. The depth doses associated with a 50-MeV cyclotron using the $d^+ \rightarrow \text{Be}$ process or high-energy cyclotrons using the $p^+ \rightarrow \text{Be}$ process rival those of a linear accelerator in the 4- to 6-MeV range. The acceptable depth doses associated with neutron machines are to some extent a function of the long treatment distances used, which are usually 100 to 140 cm. This distance is necessitated by the collimator, which must be thick because it is made of a hydrogenous material to absorb the neutrons and a metal such as lead to remove the $\gamma$-ray component.

The First Clinical Use of Neutrons

The first clinical trial of neutrons was not based on any radiobiologic rationale but was prompted largely by the availability of a new and unique beam (Fig. 24.4). It is said that it received some impetus when the mother of the Lawrence brothers (E. O. Lawrence was the inventor of the cyclotron and the director of what was to become the Lawrence Berkeley Laboratory) contracted cancer, which was judged by her physician to be incurable by conventional means. She was treated with neutrons and lived for many years, although from a retrospective review of the case it is probable that she did not have cancer in the first place. This early effort at Berkeley was hampered because the complexities of the relationship between RBE and dose for high-LET radiations were not understood at the time. Consequently, a number of patients were overdosed seriously before the trial was
terminated by the entry of the United States into World War II. In reviewing their experience many years later, Stone concluded in his famous Janeway Lecture of 1948 that “neutron therapy as administered by us resulted in such bad late sequelae in proportion to a few good results that it should not be continued.”

The Hammersmith Neutron Experience

The renewed interest in neutrons in the postwar years originated at the Hammersmith Hospital in London, where neutrons were generated by the Medical Research Council’s 60-inch cyclotron. In this machine, 16-MeV deuterons incident on a beryllium target produced neutrons with a modal value of 6 MeV. The Hammersmith cyclotron was suggested and conceived by Gray, based on the notion that a lowered OER would be advantageous to radiotherapy. The machine suffered from the limitations of poor depth doses (equivalent to 250 kVp x-rays) and a fixed horizontal beam.

A prospective randomized clinical trial to compare neutrons with x-rays was started in 1971. Advanced tumors of the head and neck were chosen because the poor depth–dose characteristics made neutrons suitable only for treating relatively superficial lesions. The trial involved patients with tumors of the salivary glands, buccal cavity, hypopharynx, and larynx.

The neutron treatments delivered in only 12 fractions were clearly superior as judged by local control of the primary tumor, but there is some question that the gain might have been achieved at the expense of a higher complication rate.

The United States Neutron Experience

Because of the limitations associated with low-energy cyclotrons, interest in a number of centers in the United States turned to the use of large cyclotrons that accelerate deuterons to energies of 22 to 50 MeV. Several such machines were built for high-energy physics research and were converted for part-time neutron therapy. In addition, neutrons were produced at the Fermilab in Batavia, Illinois, by bombarding a beryllium target with 67-MeV protons.
The early U.S. neutron therapy experience was accumulated in these four facilities. All had adequate dose rates and quite good depth doses. Unfortunately, they had disadvantages: All machines had fixed horizontal beams, and all were located in physics installations rather than in large busy hospitals, so that the availability of a sufficient number of patients was a problem. A number of controlled clinical trials were performed for a variety of tumor sites and showed no advantage for neutrons over x-rays. Neutrons, however, appeared to be superior for salivary gland tumors, soft-tissue sarcomas, and prostate cancer.

**Current Efforts with Neutrons**

Enthusiasm for neutron therapy certainly has waned just at a time at which technology allows machines to be built that are suitable for clinical use. The new generation of hospital-based cyclotrons, using the \( p^+ \rightarrow Be \) reaction has adequate dose rates, good percentage depth doses, and a full isocentric mount, similar to a conventional Linac. A few centers operate such machines in the United States, Europe, and Japan. A fair test now should be possible of neutrons compared with x-rays without the high-LET radiation being handicapped from the outset by limitations of access or physical specifications. Emphasis will be placed on two factors. First, subgroups of patients with specific types of tumors that may benefit from neutrons must be found. It is already reasonably clear that there is not an across-the-board benefit from neutrons, which was expected, perhaps naively, in the early days. Second, different fractionation patterns will be tried for neutrons. There is no a priori reason to expect that the best or most effective fractionation pattern and overall time are the same for neutrons as for x-rays. Indeed, the contrary is likely to be the case, and different fractionation regimens will be tried, especially smaller numbers of fractions in a shorter time (i.e., accelerated treatment).

Emphasis will be placed on slowly growing tumors, in view of the observation of Breuer and Batterman that neutron RBE, measured from pulmonary metastases in patients, increases as tumor volume doubling time increases (Fig. 24.5). This coincides with the

**Figure 24.5.** Values of relative biological effectiveness (RBE) relative to cobalt-60 \( \gamma \)-rays for volume changes of pulmonary metastases in patients as a function of the volume doubling time. Dots indicate the measured RBE values; open circles are estimated values if only neutron irradiation was given. (From Batterman JJ: Clinical Application of Fast Neutrons: The Amsterdam Experience, p 43. Amsterdam, Rodopi, 1981, with permission.)
clinical experience that neutrons appear to be superior for prostate and salivary-gland tumors and soft-tissue sarcoma—all relatively slowly growing tumors.

**BORON NEUTRON-CAPTURE THERAPY**

The basic idea behind boron neutron-capture therapy (BNCT) is elegant in its simplicity. It has appealed to physicians, and particularly to physicists, for the best part of half a century. The idea is to deliver to the cancer patient a boron-containing drug that is taken up only in tumor cells and then to expose the patient to a beam of low-energy (thermal) neutrons that themselves produce little radiobiologic effect but that interact with the boron to produce short-range, densely ionizing \(\alpha\)-particles. Thus, the tumor is intensely irradiated, but the normal tissues are spared. There are two problems inherent in this idea that have so far proved to be intractable:

1. How does one find a “magic” drug that can distinguish malignant cells from normal cells? (The skeptic might add that searching for such a drug has been the Holy Grail of cancer research and that if one were found, the obvious strategy would be to attach an alkylating agent or an \(\alpha\)-emitting radionuclide to it; combining its use with neutrons would be a distant third.)

2. The low-energy neutrons necessary for BNCT are poorly penetrating in tissue and consequently result in percentage depth doses that are horrible by today’s standards.

A number of nuclides have high propensities for absorbing low-energy or thermal neutrons; that is, they have a high neutron-capture cross-section. Boron is the most attractive of these because it is readily available in a nonradioactive form, its chemistry is such that it can be incorporated into a wide variety of compounds, and if it interacts with low-energy neutrons it emits short-range, high-LET \(\alpha\)-particles.

For BNCT to be successful, the compounds to be used should have high specificity for malignant cells, with concomitantly low concentrations in adjacent normal tissues and in blood. This, of course, is a tall order.

In the early days, the compounds used were not specially synthesized for BNCT but were already available. In the brain, which is the site for which BNCT largely has been used, some selectivity is obtained because compounds do not penetrate normal brain tissue to the same degree as brain tumors in which the blood–brain barrier is absent or severely compromised.

**Boron Compounds**

Critical to the success of BNCT is the requirement that boron compounds be developed that target tumor versus normal cells selectively, achieve a sufficient concentration within the tumor, and produce tumor to normal tissue ratios of 3 or 4 to 1. This, of course, is a tall order.

Two classes of compounds have been proposed:

1. Low molecular weight agents that simulate chemical precursors required for tumor cell proliferation have the ability to traverse the cell membrane and be retained intracellularly. Two boron compounds have been identified and used clinically, known as BSH and BPA. Both have been used to treat brain tumors, and the latter also has been listed for cutaneous melanoma.

2. High molecular weight agents such as monoclonal antibodies and bispecific antibodies have been developed that contain boron. These are highly specific, but very small amounts reach brain tumors following systemic administration. Boron-containing conjugates of epidermal growth factor, the receptor for which is overexpressed on some tumors including glioblastoma, also have been developed.

If the blood–brain barrier is disrupted temporarily, these high molecular weight com-
compounds may have some utility, or direct intra-
cerebral delivery may be required. They have
not yet proved to be effective in clinical use.

Neutron Sources

During fission within the core of a nuclear
reactor, neutrons are “born” that have a wide
range of energies. Neutron beams can be ex-
tracted from the reactor by the application of
suitable techniques and the use of appropriate
moderators. Thermal neutrons, or room-tem-
perature neutrons (0.025 eV), react best with
boron to produce densely ionizing α-particles.
Unfortunately, thermal neutrons are at-
tenuated rapidly by tissue; the half-value layer
is only about 1.5 cm. Consequently, it is not
possible to treat to depths of more than a few
centimeters without heavily irradiating sur-
face normal tissues. Nevertheless, most clini-
cal trials in Japan have utilized neutrons of
this energy.

Current interest in the United States fo-
cuses on the use of epithelial neutron beams
(1–10,000 eV), which have a some-
what greater depth of penetration. These can
be obtained by using moderators or filters to
slow the fast neutrons into the epithelial
range and filtering out the residual thermal
neutrons. These epithelial neutrons do not
themselves interact with the boron but are
degraded to become thermal neutrons in the
tissue by collisions with hydrogen atoms.
Even so, the peak in dose occurs at a depth
of only 2 to 3 cm, with a rapid fall-off be-
bonding this depth. Thus, the very high surface
doses are avoided but the depth doses are
still poor.

The need for a nuclear reactor as a source
of neutrons is a serious limitation and would
preclude BNCT facilities in densely popu-
lated urban areas. If BNCT were shown to
have a clear therapeutic advantage, then it
would be essential to design and build com-
 pact proton accelerators as a source of neu-
trons. Some research has been performed in
this area, and it is clear that appropriate ac-
celerators could be produced commercially if
the demand were there.

Clinical Trials

A number of clinical trials have been per-
formed over the years, beginning in the 1950s
and 1960s. Results are tantalizing but never
definitive. In more recent years, a number
of patients have been treated with BNCT in the
United States, but the results are largely anec-
dotal. The concept of BNCT is as attractive as
ever, but it continues to be difficult to convert
into a practical treatment modality, even for
shallow tumors.

PROTONS

Protons are attractive for radiotherapy be-
cause of their physical dose distribution; their
radiobiologic properties are unremarkable.
The RBE of protons is indistinguishable from
that of 250-kV x-rays, which means that they
are 10 to 15% more effective than cobalt-60 γ-
rays or megavoltage x-rays generated by a lin-
ear accelerator. The OER for protons also is
indistinguishable from that for x-rays, namely
2.5 to 3. These biologic properties are consist-
tent with the physical characteristics of high-
energy proton beams; they are sparsely ioniz-
ing, except for a very short region at the end
of the particles’ range, just before they stop.
In the entrance plateau the average LET is
about 0.5 keV/μm, rising to a maximum of
100 keV/μm over a few microns as the parti-
cles come to rest. This high-LET component
is restricted, however, to such a tiny length of
track, and represents such a small proportion
of the energy deposited, that for high-energy
protons it does not have any significant effect.

The dose deposited by a beam of monoener-
ergistic protons increases slowly with depth
but reaches a sharp maximum near the end of
the particles’ range in the Bragg peak. The
beam has sharp edges, with little side-scatter,
and the dose falls to zero after the Bragg peak,
at the end of the particles’ range. The possi-
bility of precisely confining the high-dose re-
gion to the tumor volume and minimizing the
dose to surrounding normal tissue is obvi-
ously attractive to the radiotherapist. Protons
and helium ions come closest to realizing this
dream at modest cost.
Proton beams ranging in energy from 150 to 200 MeV are of interest in radiotherapy, because this corresponds to a range in tissue of 16 to 26 cm. Intense proton beams in this energy range are produced readily by cyclotrons, many of which were built initially for high-energy physics research.

Figure 24.6 shows the depth–dose curve for the 187-MeV proton beam from the synchrocyclotron at Uppsala, Sweden. The sharply defined Bragg peak occurs at a depth in tissue that depends on the initial energy of the particles.

The early medical use of proton beams involved treatment of the pituitary, first in patients with advanced breast cancer and later in patients with diabetic retinopathy, Cushing's disease, and acromegaly. Protons were used for these applications to exploit their well-defined beam, which made it possible to give a large dose to the pituitary without causing unacceptable damage to nearby structures. These treatments have been performed at both Berkeley and Harvard, although the two institutions adopted very different strategies. At Harvard, an attempt was made to use a narrow pencil beam of protons of just the right range for the Bragg peak to fall exactly in the pituitary; in this way a huge local dose could be delivered to the gland with minimal irradiation of surrounding tissues. This would appear to be a very elegant approach to the problem, but it is fraught with difficulty because the exact location of the Bragg peak can vary considerably with small inhomogeneities in the tissue traversed. For this reason the Berkeley group favored the use of the plateau portion of a very high-energy beam that passed right through the patient's head; the Bragg peak was not within the patient at all. Multiple beams then were used in a pseudorotation technique, converging on the pituitary, to obtain good dose localization.

The way in which the Bragg peak can be spread out to encompass a tumor of realistic size is illustrated in Figure 24.7. In this figure, curve A shows the narrow Bragg peak of the primary beam of the 160-MeV proton beam at the Harvard cyclotron. Beams of lower intensity and shorter range, shown in curves B, C, D, and E, are readily obtainable by passing the beam through a rotating wheel with plastic sectors of varying thickness. The composite curve, S, which is the sum of all the individual Bragg peaks of the beams of varying range, results in a uniform dose over 2.8 cm. The spread-out Bragg peak, of course, can be made narrower or broader than this, as necessary.

Many researchers consider protons to be the treatment of choice for choroidal melanoma. Figure 24.8 shows the dose distribution that is achieved at the Harvard cyclotron, which allows very high doses to be delivered to small tumors without unacceptable damage to nearby normal tissues. Protons have found a small but important place in the treatment of ocular tumors and also some specialized tumors close to the spinal cord.

Broad-beam radiotherapy, with the Bragg peak spread out to cover a large tumor, has been in progress at Uppsala since 1957, and a comparable U.S. effort has begun at Harvard. Protons seldom are used alone in such applications because there is no skin-sparing ef-
of protons.

The way a proton beam is used to the surrounding tissue is a very
but it is exact...
the tissue...tion of a used right Bragg peak.
Multiple rotation ary, to ob-

peak can be of realistic this fig-

Figure 24.7. The way in which the Bragg peak for a proton beam can be spread out. Curve A is the depth-dose distribution for the primary beam of 160-MeV protons at the Harvard cyclotron, which has a half-width of only 0.6 cm. Beams of lower intensity and shorter range, as illustrated by curves B, C, D, and E, can be added to give a composite curve S, which results in a uniform dose over 2.8 cm. The broadening of the peak is achieved by passing the beam through a rotating wheel with sectors of varying thickness. (Adapted from Koehler AM, Preston WM: Radiology 104:191–195, 1972, with permission.)

Figure 24.8. Dose distribution used for the treatment of choroidal melanoma at the Harvard cyclotron. Note the sharp edges to the beam and rapid falloff of dose outside the treatment volume. (Courtesy of Dr. Herman Surt.)
fect, but rather they are mixed with high-energy x-rays. This is highly experimental and has shown no obvious advantage, so that the use of protons appears to be limited to those specialized situations in which a sharply defined high-dose region with rapid fall-off of dose is important.

By January 1998, a total of over 20,000 patients had been treated with proton beams, with close to half of them treated at the Harvard cyclotron, operated by the Massachusetts General Hospital. Table 24.1 lists the current and planned proton-therapy facilities worldwide.

Most of the proton machines used in the past were built initially for physics research and were located in physics laboratories. There is much current interest in the development of hospital-based proton facilities producing beams sufficiently penetrating to make possible the treatment of any cancer sites in the human, including a gantry with an isocentric mount, and feeding several treatment rooms. The first machine of this kind was built at Loma Linda University in California, where a 250-MeV cyclotron produces a proton beam that can be directed into any one of four treatment rooms. The layout of the facility is shown in Figure 24.9. The intention is to treat a broad spectrum of human cancers, not just the limited sites for which the dose distributions possible with protons already have proved their worth.

An even more impressive facility has been completed at the Massachusetts General Hospital in Boston. As already mentioned, this group has treated more patients with protons than anyone else in the world, but whereas formerly they used a fixed horizontal beam from a cyclotron in the Harvard Physics Department, they now have a new facility constructed within the hospital. Similar facilities are being built or are in the planning stage at several places in the United States, Europe, and Japan. Such facilities set the scene for the future.

### Table 24.1. Worldwide Proton Facilities and Patient Totals (as of January 1998)

<table>
<thead>
<tr>
<th>Who</th>
<th>Where</th>
<th>What</th>
<th>Date First Rx</th>
<th>Date Last Rx</th>
<th>Recent Patient Total</th>
<th>Date of Total</th>
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<tbody>
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<td>p</td>
<td>1954</td>
<td>1957</td>
<td>3</td>
<td>June 1991</td>
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<tr>
<td>Berkeley</td>
<td>California</td>
<td>He</td>
<td>1957</td>
<td>1992</td>
<td>2,054</td>
<td>January 1996</td>
</tr>
<tr>
<td>Dubna</td>
<td>Russia</td>
<td>p</td>
<td>1967</td>
<td>1974</td>
<td>84</td>
<td>January 1996</td>
</tr>
<tr>
<td>Moscow</td>
<td>Russia</td>
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<td>1996</td>
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</tr>
<tr>
<td>St. Petersburg</td>
<td>Russia</td>
<td>p</td>
<td>1975</td>
<td>1996</td>
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<td>Chiba</td>
<td>Japan</td>
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<td>1984</td>
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<td>1993</td>
<td>1996</td>
<td>1</td>
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</table>

Based on Particles, a newsletter sponsored by the Proton Therapy Cooperative Group. Rx, Radiotherapy; p, proton; He, helium ion.
Figure 24.9. Model of the proton facility at Loma Linda. Protons are accelerated to energies up to 250 MeV in a large cyclotron. The protons then can be directed into any one of four treatment rooms. This arrangement minimizes "idle" time, because while one patient is being treated in one room the next two patients can be set up in adjoining treatment rooms. This sort of facility sets the scene for the future, that is, a large radiation-therapy facility with multiple treatment rooms in the context of a cancer center. (Courtesy of Drs. James Slater and John Archambeau, Loma Linda University, Loma Linda, California.)

SUMMARY OF PERTINENT CONCLUSIONS

Neutrons

- Neutrons are indirectly ionizing. In tissue they give up their energy to produce recoil protons, α-particles, and heavier nuclear fragments.
- Biologic properties differ from x-rays in several regards: reduced OER, little or no repair of sublethal damage or potentially lethal damage, and less variation of sensitivity through the cell cycle.
- The rationale for the use of neutrons in radiotherapy has changed over the years. The earlier rationale was the reduced OER to overcome the problem of hypoxic cells. The revised rationale is based on a higher neutron RBE for slowly growing tumors.
- An advantage has been proved in clinical trials for neutrons in the treatment of salivary-gland and prostate tumors and soft-tissue sarcomas, but not for the majority of cancer sites tested.
- A new generation of hospital-based cyclotrons, generating neutrons by the $p^+ \rightarrow \text{Be}$ reaction, are now in use.

Boron Neutron-capture Therapy

- The principle is to deliver a drug containing boron that localizes only in tumors and then to treat with low-energy thermal neutrons that interact with boron to produce α-particles.
- Boron is a suitable substance because it has a large cross-section for thermal neutrons and emits short-range densely ionizing α-particles if bombarded by thermal neutrons. Its chemistry is such that it can be incorporated into a wide range of compounds.
Many attempts have been made to synthesize boron-containing compounds that are selectively localized in tumors relative to normal tissues, with limited success. They fall into two categories:
1. Low molecular weight agents that simulate chemical precursors needed for tumor proliferation
2. High molecular weight agents such as monoclonal antibodies.
• Thermal neutrons are poorly penetrating in tissue, with a half-value layer of only 1.5 cm.
• Epithermal neutrons are somewhat more penetrating. They are degraded to thermal neutrons by collisions with hydrogen atoms in tissue. The peak dose is at 2 to 3 cm, and the high surface dose is avoided.
• Results of clinical trials of the efficacy of BNCT are tantalizing but not definitive.
• The concept of BNCT is very attractive, but formidable practical difficulties are involved in making it a practical treatment modality even for relatively shallow tumors.

Protons
• Protons result in excellent physical dose distributions.
• Protons have biologic properties similar to x-rays.
• There is an established place for protons in the treatment of choroidal melanoma or tumors close to the spinal cord, in which a sharp cutoff of dose is important.
• Hospital-based high-energy cyclotrons with isocentric mounts are being used to treat a broader spectrum of cancer patients with protons. Their efficacy has yet to be proven.

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