2 Accelerators for Medicine

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2.1 Introduction

A few months after Röntgen's discovery of X-rays in the autumn of 1895, this new type of radiation was already being made use of in attempts to treat malignant tumors in patients. Starting during the 1910s, radium was also used for cancer treatment, both in "brachytherapy" with the sources near ("brachy") the tumor and with the radium sources outside the body (teletherapy). The main gamma rays from ^{226}Ra range between 0.24 and 2.20 MeV, i.e. they were of higher energy than the X-rays available and therefore penetrated deeper into the body of the patient. At the beginning of the 1950s, the use of radioactive ^{60}Co sources for therapy began. ^{60}Co emits gamma rays with energies of 1.17 and 1.33 MeV.

As is mentioned in Chap. 1, a few years after Robert Van de Graaff's first demonstration of the electrostatic accelerator, such a machine had already been installed at Harvard Medical School in Boston, USA [1]. This first medical machine, designed by John Trump and Robert Van de Graaff, was an open-air accelerator; a sketch is shown in Fig. 2.1. The second hospital electrostatic machine came in 1940 and was pressure-insulated. During the 1950s, around 40 electrostatic accelerators of 2–3 MV accelerating potential were delivered to different hospitals.

Starting in 1936, Lawrence used one of his cyclotrons to accelerate deuterons to 8 MeV and in this way provided most of the world's supply of artificial radioactive isotopes at that time. The accelerator was also a good neutron source, and in 1938 the first cancer patient had already been treated with neutrons obtained by use of a (d, n) reaction on a Be target from one of Lawrence's cyclotrons. A photo of his 60 inch cyclotron is shown in Fig. 2.2. Presently, more than 15 000 patients have been treated with neutrons, mainly thermal neutrons, at various places in the world. Today there are, however, only a few indications left for neutron therapy, such as radioresistant and slowly growing tumors. Experience shows that fast neutrons should be used in these cases. As there has not been any great breakthrough in neutron therapy, the number of medical neutron facilities is now decreasing drastically.

At the end of the 1940s, the newly introduced betatron was used for the first time for radiation therapy, with X-rays generated by a beam of 20 MeV

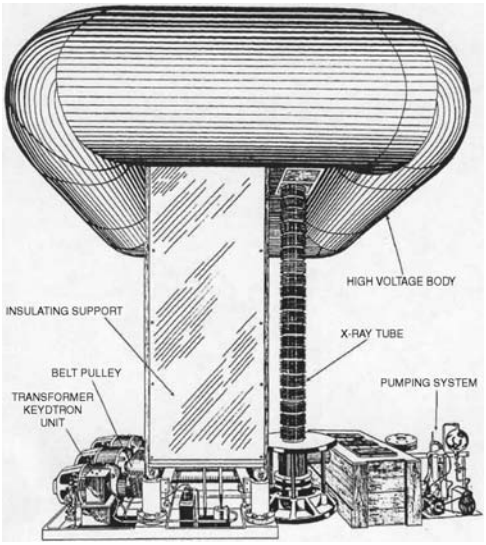

Fig. 2.1. The Trump–Van de Graaff X-ray generator installed at the Harvard Medical School (Reprinted from [1]; copyright 1937, with permission from APS)

Fig. 2.2. The newly completed 60 inch cyclotron. Ernest Lawrence is second from *left* on the floor, and Luis Alvarez and Edvin McMillan are on *top* of the machine (Reprinted with permission from LBL)

electrons. Betatrons played a significant role for several years, since they delivered X-ray beams (up to over 40 MeV) with better properties than those obtained from X-ray tubes and radionuclide sources and since they could also be used for electron beam therapy. At most, about 200 betatrons were in use in hospitals at the beginning of the 1970s. The major disadvantages of betatrons were their relatively low absorbed dose rate, small treatment field size, high weight and cost.

In the early 1950s, a few RF linear accelerators were installed at hospitals. In the 1960s the number increased considerably, and soon the linac became, and still is, the dominant type of hospital-based accelerator for radiotherapy. In Fig. 2.3, a modern linac for patient treatment is shown. The rapid growth and dominant role of linacs depend on the fact that they can deliver a ten times higher dose rate compared with a betatron (several Gy/min, compared with half a Gy/min for a betatron), with a geometrical field size up to $0.4 \times 0.4\,\mathrm{m}^2$, compared with $0.1 \times 0.1\,\mathrm{m}^2$ for the betatron. Today (2004) around 5 000 medical linacs around the world are used for treating several millions of patients yearly.

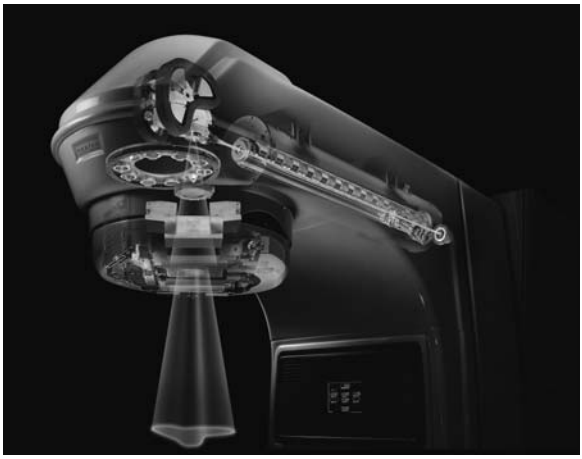

Fig. 2.3. A linac for radiotherapy equipped with a multileaf collimator. The electron beam is bent in a 270° magnet. After flattening and collimation, the electron beam can be used for treatment. In most cases, however, the electron beam collides with a heavy-metal target, and the high-energy bremsstrahlung produced is used for treatment after flattening and collimation with the multileaf collimator (Reprinted with permission from Varian Medical Systems Inc.)

The first proton beam used for treatment was obtained from a cyclotron in Berkeley, USA, and shortly after that from the synchrocyclotron in Uppsala, Sweden, at the end of the 1950s. Today there are a number of proton facilities around the world, and up to now (December 2004) 40 000 patients have been

treated. Larger use of proton therapy has been limited by the high cost of a dedicated hospital-based proton therapy unit. The cost per treatment fraction is, however, only around 70% higher than the cost of conventional photon and electron therapy [3]. At the beginning of the 1990s, the first superconducting cyclotron was taken into biomedical use. Also at the beginning of the 1990s, the first hospital-based proton synchrotron was used for therapy. Starting in 1975, in Berkeley, ions heavier than protons have also been tested for radiotherapy, with the intention of obtaining more efficient therapy for some patient groups.

Most medical accelerators are used for radiotherapy. Accelerators are also used for production of radionuclides, in the radiopharmaceutical industry or locally at hospitals, and for sterilization of medical equipment. A useful book about biomedical accelerators is found in [2].

2.2 Radiation Therapy

Radiotherapy is, after surgery, the most widely used form of cancer treatment, in Europe and the USA being given to about half of all cancer patients. There is nothing to suggest that other methods for treating cancer can replace radiotherapy in the foreseeable future. The possibility of selectively destroying tumor cells by radiation in the presence of normal cells depends on the fact that tumor cells are more sensitive to radiation than normal cells, and that the repair of malignant cells is less efficient. The difference in the effect on tumor and normal cells is – for photon and electron radiation – increased if the radiation is fractionated in time, for external-beam therapy normally into 2 Gy fractions given once a day, five days per week over a number of weeks. The objective of radiation therapy is to deliver a defined absorbed dose of radiation to a specific tissue volume – including the tumor volume and adjacent tissues where tumor cells might be found – with the intent of killing tumor cells while minimizing irradiation of surrounding, healthy tissue.

External-beam therapy is the most common form of radiotherapy. Externally produced photon beams, or X-rays, are used in more than 80% of all radiation treatments. In addition, electron beam therapy is used in 10–15% of cases. The rest are treated by brachytherapy (either intracavitary or interstitial – with the source either in a cavity or in the tumor itself), external proton therapy, therapy with radiopharmaceuticals or a limited number of other methods.

2.2.1 Electron and Photon Beams

The electron and photon (X-ray) beams are today produced by linacs, which normally offer the possibility to produce two photon energies as well as several electron energies. Typical values are 6 MV and 10, 15 or 18 MV for X-rays, and six electron energies between 6 MeV and 20 or 22 MeV.

In the linac, the accelerated electrons collide with a heavy-metal target. As a result of these collisions, high-energy X-rays are produced in the target. The electron beam itself can also be used for radiotherapy directly, after flattening. The therapy beams are shaped to match the patient's tumor. The beam comes out of a gantry, which can rotate around the patient. The patient lies on a movable treatment couch, and laser beams are used to make sure the patient is in the proper position. Radiation can be delivered to the tumor from any angle by rotating the gantry and moving the treatment couch.

The process of external-beam therapy can be divided into various parts:

- imaging as a basis for treatment
- treatment planning
- simulation of the treatment
- treatment delivery
- follow-up of treatment.

First, the tissue volume to be irradiated and the tissues to be protected must be defined. The imaging needed is done in addition to the diagnostic investigations done in connection with the patient's earlier investigations. Up to now, ordinary radiography and X-ray computed tomography (CT) have been the basis for tumor volume delineation, but positron emission tomography (PET) combined with CT (PET/CT), and magnetic resonance imaging (MRI) are more and more used. The tumor delineation is followed by treatment planning, whereby the direction and shape of the radiation beams are configured to achieve a dose distribution that corresponds as well as possible to that desired. The planning also involves the choice of the appropriate absorbed dose in the respective target volumes, the number of fractions and absorbed dose per fraction, and the total treatment time.

For treatment planning, computers are used to calculate the absorbed dose distribution that will be delivered to the patient's tumor and the surrounding normal tissue. In certain cases, this process may employ such techniques as three-dimensional conformal therapy and intensity-modulated radiation therapy.

During simulation of the treatment, the patient is placed in the treatment position on a special X-ray machine or CT scanner, and simulation X-rays are taken. X-ray images are taken in the directions of the treatment beams, including markings to indicate the size and shape of the field planned for therapy. Fixation or other devices are used to help the patient not to move during the simulation and treatment processes. The beams needed to treat the patient are tested, and small marks on the patients are made to guide the daily treatments. After possible adjustment, the parameters are transferred to the treatment unit. A schematic description of the process leading up to the treatment is shown in Fig. 2.4.

After the simulation, the treatment itself can begin. In the treatment, the patient is placed on the table top of the accelerator, exactly in the same way as in the simulator. Similarly adjusted laser light beams to those used

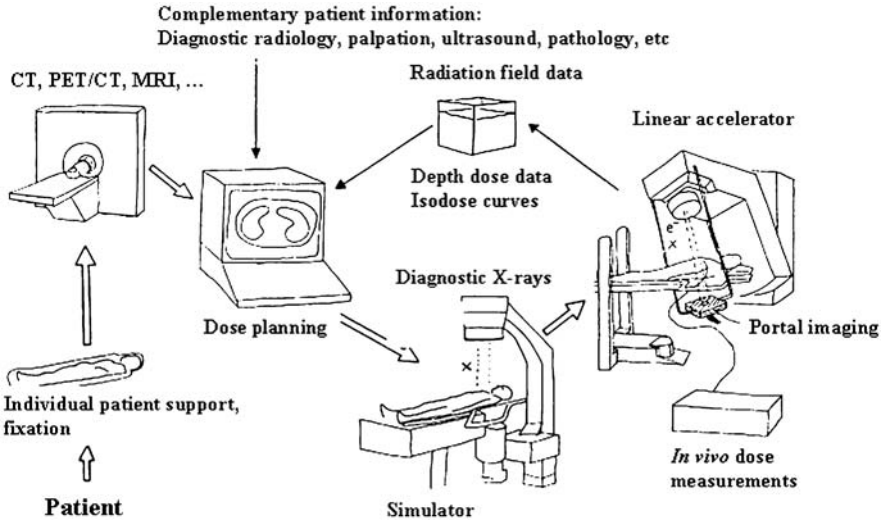

Fig. 2.4. The process of imaging, planning, simulation and treatment

at the simulator and at the diagnostic modalities used are projected onto the patient to determine the position coordinates, and a light field on the patient simulates the radiation field. The setup is checked by imaging the initial therapy radiation transmitted through the patient. New portal imaging devices make image-guided radiotherapy possible. In Fig. 2.5, the preparation just before the start of treatment is shown.

Beams from one or more directions may be used, and the beam may be on for as long as several minutes for each field. The treatment process can take from 10 to 30 min, and most of the time is often spent positioning the patient. Patients usually receive radiation treatments once a day, five days a week, for a total time ranging from two to nine weeks.

The past decade has seen a succession of advances in radiation therapy. New techniques of diagnosis are improving the possibilities for tumor delineation. The possibilities for rapid and adequate 3D treatment planning have been refined. New techniques of external radiation treatment are making possible intensity-modulated radiation beams, confining the high therapeutic dose to the target tissues. These things taken together imply increased possibilities for augmenting the effect on the tumor while at the same time reducing the risk of adverse effects in normal tissue.

The multileaf collimator (MLC) – seen in Fig. 2.3 – offers the possibility to shape the beam in conformity with the target outline (conformal therapy). Recently, intensity-modulated radiotherapy (IMRT) has been developed, giving further improved conformity.

The patient's position has to be reproduced as precisely as possible for each treatment session. Delivery of escalated absorbed doses by IMRT

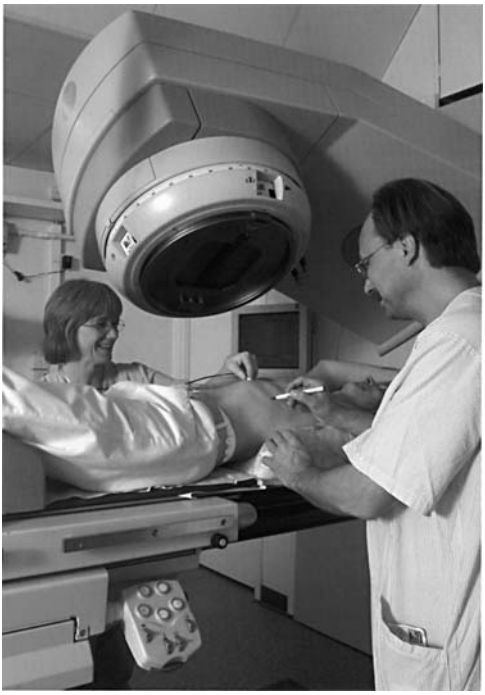

Fig. 2.5. Preparation before start of treatment by means of a linear accelerator. The patient is placed on the treatment table top and a reproducible positioning is supported by individual casts, which are used during the whole treatment series. Field markers from the simulator are checked against beam indicators. A diode dosemeter for entrance dose measurements is applied. The portal dose-imaging system is not shown. Photo from Malmö University Hospital, Sweden

necessitates knowing the exact tumor position prior to radiation treatment delivery. Tumors located in the chest, abdomen or pelvis can shift their position from day to day over the course of treatment owing to movements of internal organs and volume changes. Geometric precision better than 5 mm and absorbed-dose accuracy of better than 5% are necessary.

2.2.2 Protons and Light Ions

It was R. Wilson who first realized the medical potential of protons and carbon ions for therapy in 1946. Proton irradiation offers better dose distribution than do conventional photon and electron beams. An excellent depth dose can be reached with energy- and intensity-modulated beams from commercially available equipment. Light-ion beams have been used for treatment in two centers in Japan starting in the beginning of the 1990s and in an experimental facility at GSI in Darmstadt starting in 1997. One clinical unit is

under construction in Heidelberg. The cost of light-ion therapy is 2.5–3 times as high as that of proton beam therapy and the clinical rationale for more general use is not yet convincing [3].

2.2.3 Synchrotron Radiation

Synchrotron radiation is used today for research in biology, chemistry, physics and their numerous subfields. As is outlined in Chap. 3, the technique has had a very high impact on research in these fields. Practical applications in medicine seem, however, to be quite a way off.

The interest in synchrotron radiation for medicine is that it can be produced with such a high photon fluence rate that even after an energy selection, the fluence rate is so high that the source can be used for radiography. Another important parameter is that very narrow and parallel beams can be produced.

Several experimental approaches are being explored using synchrotron radiation to enhance the effectiveness of radiation therapy. One is the microbeam therapy technique. It is based on irradiating a tumor with multiple parallel, microscopically narrow, planar beams in the 50–150 keV range. Typically, the width of a microbeam is 25 μm and the distance between the parallel beams 200 μm. In this way, tissue necrosis on the way in to the tumor volume could be prevented. The effects in the target volume can be achieved through cross-firing.

Another approach is photon activation therapy, where a sufficiently high concentration of iodine (or other heavy element) from, for example, an X-ray contrast agent in the tumor creates Auger electrons and photoelectrons close to the tumor cells. The energy of the synchrotron radiation is chosen slightly above the K-absorption edge of the heavy element.

2.3 Production of Radiopharmaceuticals for Medical Imaging

The first radionuclide to be used for nuclear medicine was produced by a cyclotron in 1936. A few years later the first nuclear reactor was demonstrated, and radionuclides could be obtained from reactors as well. Unfortunately, only radionuclides that have an excess of neutrons can be obtained from reactors. On the other hand, all types of nuclides can be obtained from an accelerator. Another advantage of an accelerator compared with a reactor is that the compactness of the accelerator make it possible to have it installed at the hospital. Today more than 200 small compact cyclotrons with proton, deuteron and alpha energies up to 20–40 MeV and beam currents of the order of mA are used for radionuclide production. The activity which can be produced is limited, chemical separation is necessary and the production cost is

relatively high. There are also a number of requirements on the material to be irradiated: thermal conductivity, resistance to overheating and an ability to withstand vacuum. The required chemical amount of material for one investigation is very low (of the order of 10^{-7} g), and much less than that required for chemical synthesis. The production of radionuclides is today dominated by (isochronous) cyclotrons. It is demonstrated in Chap. 19 that dedicated electrostatic accelerators can also play an important role today in the production of short-lived nuclides. If a radioactive material is administered to a patient, the emitted radiation can be detected outside the body (if the energy is high enough) in different directions. Compared with diagnosis with X-rays, this nuclear medical technique is not used so often, even if around 20 million investigations are done per year in the world.

Positron emission tomography (PET) is a powerful diagnostic tool in modern medical imaging. It uses short-lived radionuclides such as ^{18}F (physical half-life 110 min), ^{11}C (20 min), ^{13}N (10 min) and ^{15}O (2 min), which can be produced by low-energy cyclotrons (< 20 MeV) accelerating protons and/or deuterons.

Most cyclotrons either are placed at a hospital or are part of a commercial company. The hospital is interested in a continuous supply of ^{18}F–FDG to use for tumor scintigraphy and delineation. A few large research machines are also employed in nuclide production, such as isochronous cyclotrons, ion RF linacs and tandem accelerators. As an example of the development at a research accelerator, the production of ^{123}I, with half-life 13.2 h, by a large research linac has initiated other large facilities to start a similar production. The ^{123}I competes favorably with the ^{131}I used earlier, with half-life 8.05 d, as the dose to the patient decreases by a factor of 50 to 100 when ^{131}I is replaced with ^{123}I.

2.4 Analytical Applications

The uses of MeV ion beams from electrostatic accelerators for studies of chemical composition, atomic structure, and surface or near-surface layers are analytical techniques which have developed rapidly during the last ten to twenty years. These techniques have mostly been used for studies of materials and solid state physics. Only during the last 10 years have these techniques also been enlarged to include medical investigations. The relative sensitivity of some of these methods is 10^{-6} or even less, and the depth resolution of some of them is down to tens of nm. The analysis time per sample is of the order of tens of minutes and the amount of material necessary is often less than 1 mg. The most well-known techniques are PIXE (particle-induced X-ray emission), RBS (Rutherford backscattering) and NRA (nuclear reaction analysis). These techniques are described in detail in Chaps. 24, 25 and 26. By using a beam with a diameter down to 1 μm, microscopy methods can be

applied with these methods. In biomedical applications, this makes it possible to analyze tissue, subcellular and cellular structures.

Accelerator mass spectrometry (AMS) is an ultrasensitive technique which has found its main application in the quantification of very rare long-lived radionuclides. For details about AMS, see Chap. 23. The most well-known example is ^{14}C (10^{-10}% of the carbon in living organisms is ^{14}C). Unlike a detector for the measurement of radioactivity, a mass spectrometer does not have to wait for the nuclide to decay. Thus, in the case of ^{14}C, AMS is about 1000 times more sensitive than any radiometric method (out of 10^9 ^{14}C atoms, only about 10 will decay during one hour). AMS has the outstanding ability to quantify ^{14}C-labeled substances down to levels of 10^{-18} moles, which is of the order of only one million molecules. The fact that AMS counts atoms and not decays results in some powerful advantages over radiometric techniques, such as highly reduced sample sizes and shortened measuring times. The potential of ^{14}C AMS for biomedical investigations is illustrated in Fig. 2.6, which shows the specific activity in exhaled air after intake of a test amount of ^{14}C-labeled fat [4, 5]. Using AMS, it is possible to follow the exhalation of increased amounts of ^{14}C for years. Using liquid scintillation counting, the exhalation could only be followed for some days. Thanks to AMS, a fine structure in the exhalation pattern due to provocation in the form of 32 h of fasting could also be clearly seen and the increased exhalation quantified.

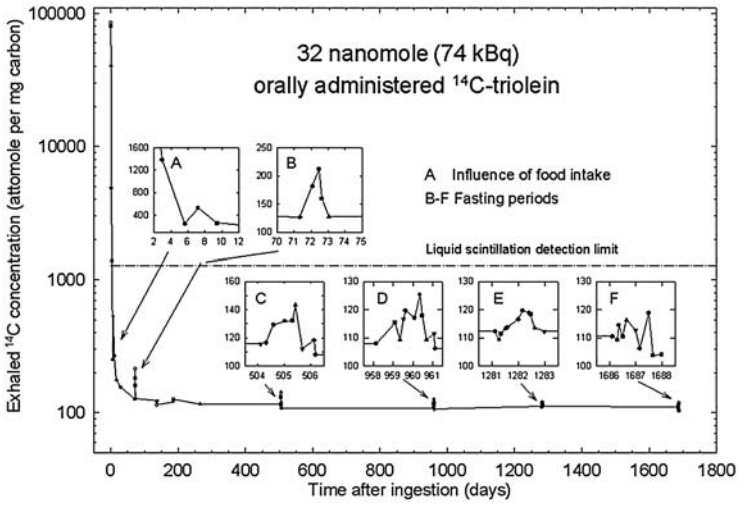

Fig. 2.6. The ^{14}C concentration in exhaled air from one volunteer at various times after oral administration of 32 nanomoles ^{14}C-triolein. The dip in the curve after 6 days (**A**) was the result of an excessive intake of food prior to sampling. This observation initiated 32 hour-long, controlled fasting periods (**B**, **C**, **D**, **E** and **F**). Data from [4, 5]

2.5 Imaging with Synchrotron Light

Over the last few years, several studies have shown the potential of synchrotron radiation for medical imaging. Mammographic images acquired with synchrotron radiation have been reported to provide a better contrast of breast lesions and a relevant reduction of the dose to the breast tissue. In angiography using X-ray contrast, one image is taken with the energy just over the absorption edge of iodine and another image with the energy just below the absorption edge. After subtraction of the images, the vessels are clearly seen. Studies have shown that the same image quality can be produced for half the dose compared with conventional techniques.

The technique can of course never be an alternative to conventional X-ray imaging, owing to the extremely high cost of a synchrotron light source.

2.6 Industrial Applications – Sterilization and Disinfection

In 1896, it had already been found that microorganisms died when irradiated with X-rays. Unfortunately, it took more than 50 years before a radiation facility was put into operation during the 1950s for sterilization of surgical threads. Electrostatic accelerators and linacs, as well as facilities equipped with gamma sources, were used. Syringes, needles, catheters and infusion sets are examples of disposables suitable for radiation sterilization. To bring down the production cost, the disposables are usually manufactured from a plastic which cannot be sterilized by heat, as they do not tolerate the necessary temperature: steam at 150°C or hot air at 200°C. The competitive methods are, of course, various chemical sterilization techniques. A major advantage of radiation sterilization is that the production process and packaging can be performed under nonsterile conditions. The final products in their cartons can be sterilized either by the manufacturer itself or by a separate company. Sterilization is today mainly done by electron beams from accelerators. High-energy bremsstrahlung X-rays from these accelerators can also be used, as well as ^{60}Co gamma sources (up to a few times 10^{16} Bq). Economically, accelerators seem to compete well with gamma sources, as the dose rate and therefore the throughput are considerably higher for an accelerator.

Typically, a dose of 20–30 kGy is used. This is obtained from an accelerator in a fraction of a second, whereas a ^{60}Co source needs to be used for hours. Electron accelerators for industrial use, including sterilization of medical disposables, food sterilization and material treatment (improvement of properties of polymer materials), are discussed in detail in Chap. 28.

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