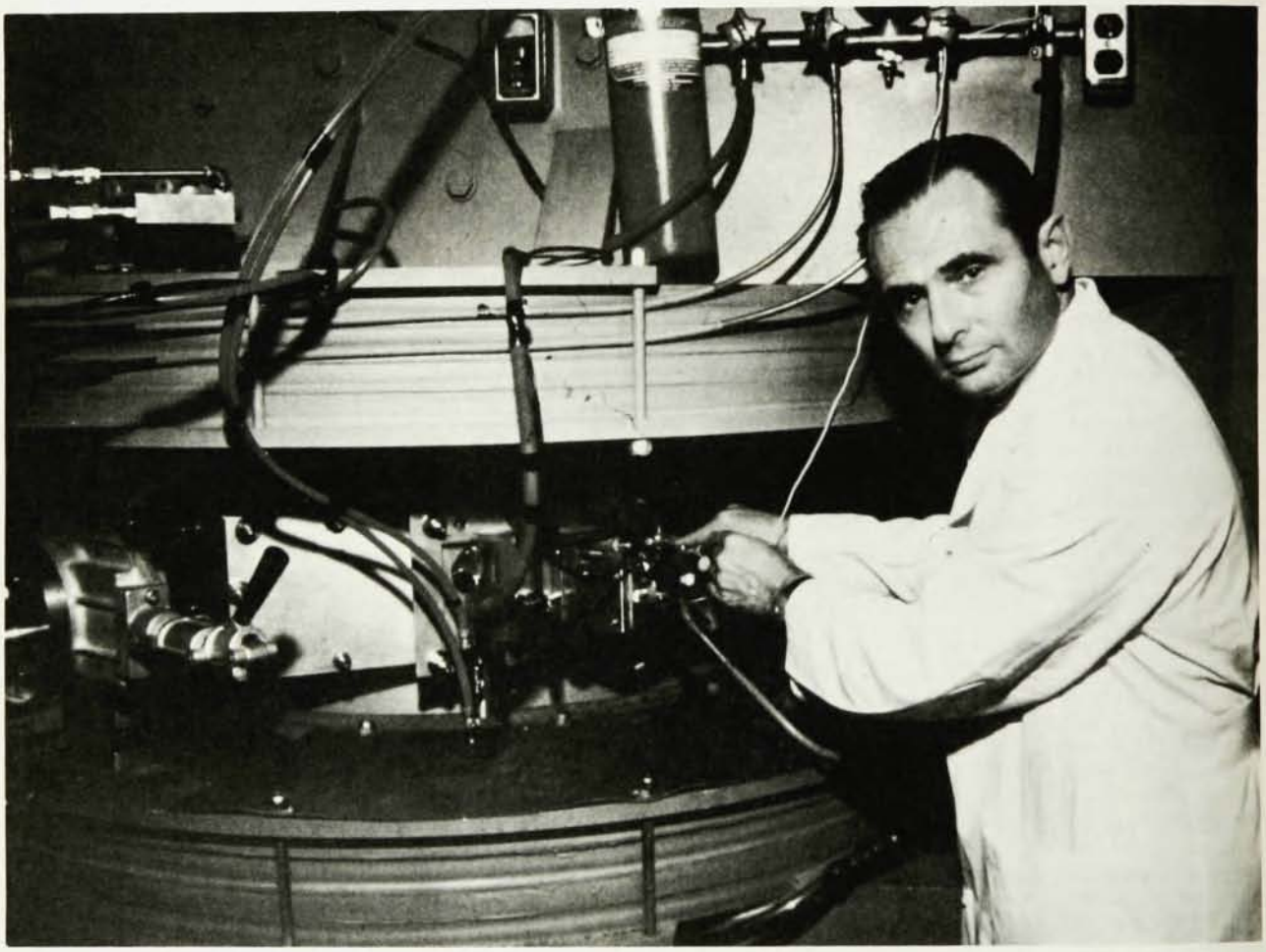
History of medical physics

Physicists applied many of their most important discoveries to medicine immediately, laying the foundation for today's radiation therapy, nuclear medicine and diagnostic radiology.

John S. Laughlin



First medical cyclotron in a US hospital. Photo shows Michel Ter-Pogossion with his cyclotron at the Mallinckrodt Institute of Radiology, Washington University, St. Louis, Missouri. The machine was installed specifically for medical research and applications. Figure 1

On the occasion of the 25th anniversary of the American Association of Physicists in Medicine, it is appropriate to look at the history of the field of medical physics. This is not to imply that the history of the AAPM and the history of the field of medical physics are synonymous, but the latter does help us understand the former: By examining the history of physicists' scientific contributions to medicine, we will see how it was natural for the growing numbers of physicists involved to form a suitably oriented physical society.

Many tools and methods first developed in the physics laboratory are now used on a routine basis in medical laboratories and offices. For instance, one now finds atomic absorption units and spectrophotometers in most biomedical laboratories. The physician uses

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instruments and procedures derived from an understanding of mechanics, heat, light and sound to examine the eyes, to measure hearing, to perceive respiration, and to make many other basic measurements of the body.

While the term "medical physics" is broad and refers to the application of principles of physics to any aspect of medicine, for historical reasons the AAPM and similar organizations in other countries have been largely concerned with the uses of radiation—in diagnosis, treatment, research, and protection in medical institutions. In this article we will trace the development of the basic radiation physics that underlies much of today's medical physics, and then we will look separately at the historical development of two major subfields of medical physics—radiation therapy and nuclear medicine. The article beginning on page 36 of this issue covers another important subfield of medical physics, diagnostic radiology.

Medical physicists use the term radiation to cover not only ionizing radiation but some nonionizing radiations, the entire electromagnetic spectrum, and sound as well. Most of the applications of radiation physics have been in the clinical disciplines of radiation therapy, diagnostic radiology and nuclear medicine, but there have been many applications in radiobiology and radiation protection as well. Scientists sometimes refer to much of the work in diagnostic radiology and nuclear medicine as medical imaging. This terminology can have the disadvantage of focusing attention on anatomical structure, but not on studies of physiological and biochemical function with which these disciplines are also concerned.

Before we consider some of the applications of physics in radiation medicine, let us follow the historical development of the basic physics that came to be applied in hospital laboratories and clinics. Most of this work took place in university laboratories, but some of it was done in industry. We will take a more or less chronological approach, which may lead to some discontinuities, but will illustrate inadvertent interdependences of seemingly unrelated developments.

Limitations of space prevent discussion of the role of physicists in radiation biology and radiation protection, the study of which commenced on an anecdotal basis in 1896 and systematically in 1901 with the description of physiological effects of radium by Henri Becquerel and Pierre Curie.[1] The attention of radiological physicists to these matters over the decades has contributed to the excellent record of successful radiation control in medical practice. The biological effects of radiation are probably better understood, and certainly more fully characterized, than are the effects of other common agents in our environment. Our emphasis on radiation should not be taken to minimize the significance in medicine of fundamental research carried out in areas of biophysics not involving radiation, for there is much important work underway on topics such as nerve conduction, the biophysics of large molecules, and biomedical engineering.

Radiation physics emerges

Wilhelm C. Roentgen's discovery in late 1895 of the highly penetrating "new rays" was certainly a major scientific finding that has had a continuing impact in medicine. Working with a Hittorf–Crookes tube at the University of Würzburg, he observed fluorescence in crystals of barium platinocyanide located at too great a distance from the tube to fluoresce due to the known properties of cathode rays; these had been described earlier by Philip Lenard. Roentgen systematically investigated the penetration of these new rays in different materials, recorded their absorption shadows on photographic plates, and determined that their intensity decreased inversely as the square of the distance from the tube. His discovery attracted immediate attention, and within two weeks he made a personal demonstration at the request of Kaiser Wilhelm II. The vitality of communication was such that the details of Roentgen's discovery were described in Paris in late January 1896, at a meeting of the French Academy of Sciences.

This finding led in turn to the discovery of natural radioactivity by a physicist in the Paris audience, Henri Becquerel. He assumed that the fluorescence of the glass tube wall produced the x rays. Becquerel postulated that the intense phosphorescence of crystals of potassium uranyl sulfate exposed to sunlight might also be a source of x rays. But when he developed photographic plates upon which he had placed the uranium sulfate, without the benefit of sunlight during a rainy period in Paris, he observed the same darkening as with sunlight. He recognized and reported that there was a spontaneous and continuous emission of radiation from the uranium sulfate crystals.

Marie Curie extended this discovery in her study of the nature of "Becquerel rays" for her doctoral thesis. She assayed many materials for evidence of emission of radiation by measuring the conductivity of air with a piezo-electrometer previously constructed by her husband, Pierre. She independently discovered and reported the "radioactivity" of thorium in 1898. Through extensive chemical separations correlated with her emission measurements, she identified (and named) the new elements polonium and radium. It is interesting, and a tribute to the perception of the investigators involved, that although there is no direct relationship between the production of x rays and of natural radiation, the discovery of one set in motion events leading to the discovery of the other only 114 days later.

In 1897, Joseph John Thomson, who had postulated that the canal rays in his gaseous discharge tubes consisted of discrete particles with a negative charge, was able to report to the Royal Society that the masses of the negatively charged particles in a cathode-ray beam are about $^1/_{1837}$ those of hydrogen ions. Although he was more uncertain as to the magnitude of this ratio than the digits imply, he had identified the electron. It is of interest that Thomson, and his student Ernest-Rutherford, studied the ionization current in a gas as a function of x-ray exposure and collecting voltage. They published in 1896 the first "saturation curve," which is one of the important characterizations of any ionization chamber employed in dosimetry.

Subsequently, at the time of his discovery of the atomic nucleus in 1911, Rutherford asked a young investigator in his laboratory at Manchester to carry out an assignment that led to the founding of nuclear medicine. He asked Georg Hevesy to separate radium D (the isotope Pb^{210}) from "all that nuisance of lead." Although Hevesy was unsuccessful after a year of effort, he reached the significant conclusion that one could use radium D as a "radioactive indicator" for the presence of lead.

About a decade after Rutherford had postulated the existence of a neutral nuclear particle, scientists at Giessen observed a penetrating radiation produced when alpha particles from polonium hit boron or beryllium. This induced radiation was even more penetrating than the gamma rays from radium. Irene Curie and Jean Frederic Joliot verified the discovery and found further that the penetrating radiation expelled energetic protons from hydrogenous material. They considered this essentially a "Compton effect" of gamma rays on protons. James Chadwick at Cambridge extended the ex-

periments and—in line with Rutherford's earlier prediction—postulated in 1932 that the highly penetrating radiation consisted of neutral nucleons, which he named neutrons.

Shortly thereafter, on 10 February 1934, Joliot and Irene Curie announced in a note of fewer than 600 words in *Nature* the discovery of artificial radioactivity. They had bombarded boron with alpha particles from polonium to obtain nitrogen-13, and they had bombarded aluminum to obtain phosphorous-30; they observed the exponential decay of the new isotopes and measured their half-lives. They also produced ammonia labeled with nitrogen-13, a compound my colleagues and I produced on a medical cyclotron 37 years later in clinically useful quantities for imaging.[2]

By World War II, the artificial production of radionuclides was well understood, and they were being employed extensively in biological and clinical studies. The absorption of x rays via Compton scattering, coherent scattering, the photoelectric effect, pair production, and so forth, had been studied and characterized as functions of energy, atomic number and density. The diagnostic use of x rays was far advanced and equipment for this purpose was highly developed. Curative therapy with x rays was largely limited to superficial lesions because x-ray generators were limited to a few hundred kilovolts. However, doctors were employing radium effectively by placing it inside the body.

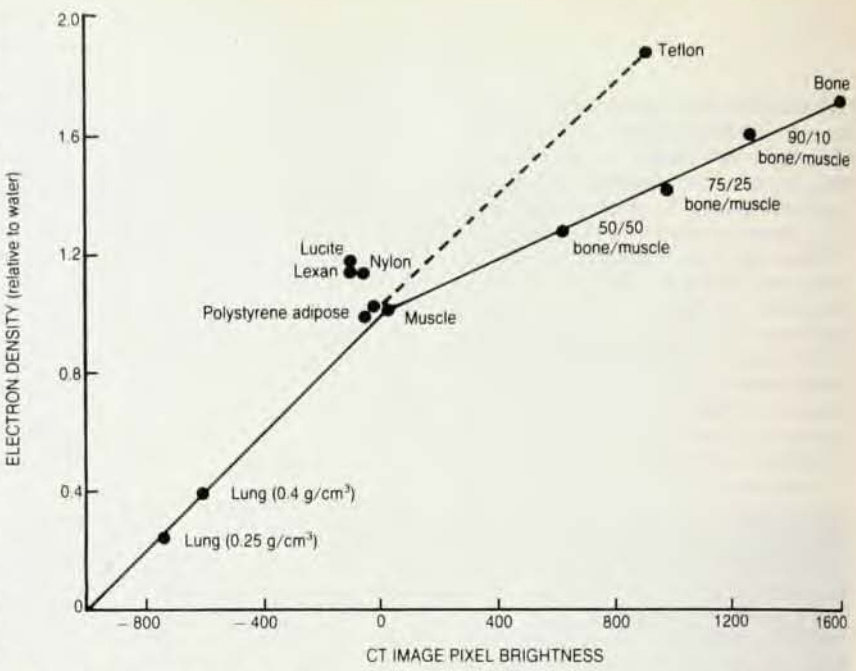
Let us look now at the connection between all the physics that we have discussed and the development of the fields of radiation therapy and nuclear medicine.

Radiation therapy

Radiation therapy includes both the administration of radiation from sources external to the body and the placement of encapsulated radioactive sources in the body. In the latter method, known as brachytherapy, sources in molds or placques are located on superficial lesions, inserted interstitially in tissue of or near the lesion, or placed into natural body cavities.

Within months after Roentgen's discovery of x rays, they were applied externally with therapeutic intent. Probably the first such application was by Emil H. Grubbé, a Chicago manufacturer of incandescent lamps and Geissler and Crookes tubes. Grubbé was also a second-year medical student, and had two cases, one neoplastic and one inflammatory, referred to him for treatment in his factory commencing in late January 1896.

Even with the further development of the Coolidge-type high-vacuum, heated-cathode x-ray tubes and reliable power supplies capable of a few hundred kilovolts, curative external radiation treatment remained limited to the more superficial lesions. It was not until physicists provided the means for accelerating electrons to energies of several million electron volts that physicians had the opportunity to use ionizing radiation for curative treatment at any site in the body.



Calibration curves showing the response of an x-ray tomograph to various test objects. One must convert computed tomography images to electron density images to predict dose distributions for x rays and electrons. The artificial substances indicated are used for calibration. (Courtesy of Mary E. Masterson, see reference 22.) Figure 2

Brachytherapy physics. Doctors first applied radiation internally through the use of radium encapsulated in needles and tubes, radon gas encapsulated in gold capillary tubing, and radioactive glass "seeds" enclosed in gold tubing. The science of the use of radium needles was developed early in many centers, particularly at the Curie Institute in Paris, the Christie Clinic in Manchester, England, the Memorial Hospital in New York, and the M. D. Anderson Hospital in Houston.

In the period 1913–17, Harvard physicist William Duane developed[3] "seeds" containing radon gas. Duane also developed a radon "plant" and a variety of techniques for using radon needles in applicators, packs and implants. In New York, Gioacchino Failla developed a radon plant of improved design at Memorial Hospital and provided radon in glass seeds or in gold capillary tubing for interstitial implants. He collaborated closely with surgeons and designed a variety of radium applicators.[4]

Radiologists in the 1930s, including Ralston Paterson and Herbert Parker at Manchester, developed[5,6] a system governing the location of radium needles. This system achieved uniform distributions of doses by using specific nonuniform distributions of sources for lesions of different sizes and configurations. At Memorial Hospital, Edith H. Quimby developed[7] an alternative system in which a uniform source distribution produced a nonuniform distribution of dose.

Although radium and radon are still employed for brachytherapy, they have been replaced largely by cobalt-60 and cesium-137 for needles and by iridium-192 and iodine-125 for seeds. The pioneering work in the use of these isotopes took place at several institutions, including Ohio State University, Memorial Hospital in New York City and the Henri Mondor Hospital near Paris.[8] Automatic computation methods developed in the 1950s at Memorial Hospital, M. D. Anderson Hospital and other institutions provide the dose distribution throughout the volume of the implant rather than at a few points.

Megavolt external sources. From the early days of radiation therapy, radiologists knew that adequate treatment with external x rays required acceleration of electrons to energies of many millions of electron volts. Originally, all differences of potential were achieved by electrostatic methods or by high-voltage step-up transformers. The insulation of the system had to sustain the full potential difference corresponding to the desired energy.

There was a clear need for an alternative approach to acceleration that would circumvent the block to adequate energies imposed by requirements of insulation and voltage enhancement. In 1924, the Swedish physicist Gustaf Ising proposed[9] a resonance method of acceleration, in which a limited potential is applied repeatedly to a given charged particle, which thereby accumulates much energy. His proposed apparatus required a linear increase in velocity with energy and was therefore not suitable to electrons of adequate energy. In 1928, Rolf Wideröe, a Norwegian physicist employed by the Brown–Boveri Company of Switzerland, reported[10] experimental achievement of resonance acceleration of sodium and potassium ions. He employed a linear array of three cylindrical electrodes with two 15-cm gaps, and an oscillator operating at a frequency of a little over 1 MHz with potential differences of 20–50 kV. In the same paper in which he reported this experiment, Wideröe proposed the "beam transformer," essentially the magnetic induction portion of the betatron, but without adequate provision for retaining the electrons in an orbit.

In 1930, Ernest Lawrence described the principle of circular magnetic resonance at a meeting of the National Academy of Sciences. He indicated that he had conceived this technique for circular resonant acceleration after reading Wideröe's paper on linear resonance acceleration. Two years later, Lawrence and Milton Stanley Livingston reported a working model that produced protons with energies of 80 000 eV using an accelerating potential of no more than 1000 volts. Stability of the hydrogen-ion trajectory in the median plane is essential and was achieved by the focusing action of a radial component of the magnetic field. As the ions attain relativistic velocities, their masses increase and they lose their phase relationship with the radio-frequency accelerating field. This limits the conventional cyclotron to approximately 25 MeV in the case of protons. One can exceed this limit by various strategems as in the synchrocyclotron or in the cyclotron with an azimuthally varying magnetic field. The term "isochronous" is applied to the latter cyclotrons because the accelerated particles circulate at a constant frequency of revolution, even at relativistic energies.

Hospitals have used cyclotrons, such as the one shown in figure 1, for the production of radionuclides, for clinical studies of neutron therapy, for proton irradiation of the pituitary and for treatment of certain superficial lesions. Some clinical studies have used heavy-ion accelerators as well.

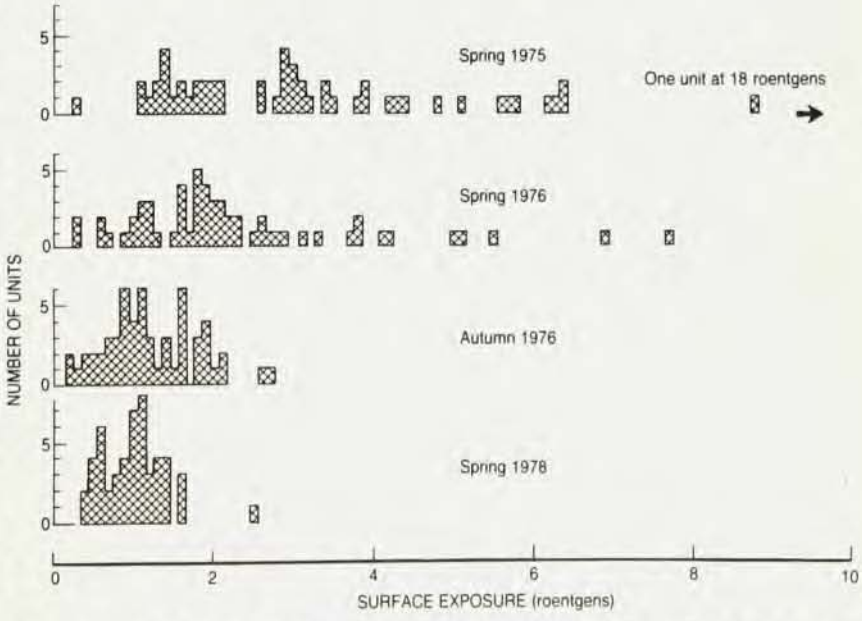
In 1940, Donald W. Kerst of the University of Illinois developed[11] the betatron. In addition to providing for an increasing magnetic flux to induce electrons to accelerate, Kerst shaped the pole faces to establish a stable equilibrium orbit. He also injected the electrons tangentially near this orbit. His first betatron operated at 2.3 MeV, the second at 20 MeV and the next at 300 MeV. The accelerated electrons had a relatively monoenergetic spectrum, and their energy was easy to vary. The target for x-ray production was mounted on the injector assembly and had such minute dimensions that the radiation field was sharply defined with no penumbra.

In 1948, a graduate student at the University of Illinois developed a glioblastoma, a serious malignant lesion in the brain, and it was decided to attempt localized irradiation following surgery. Radiologist Henry Quastler and Kerst organized this first treatment with high-energy x rays. They rapidly developed methods of dosimetry, monitoring and collimation of the fixed horizontal beam, and carried out[12] a treatment of 30 beams, or "fields." Although they delivered a tumoricidal dose out to the margins of the lesion, the patient eventually succumbed. Postmortem examination revealed no viable neoplastic cells (cells with uncontrolled growth) in the irradiated region.

The Allis–Chalmers Manufacturing Company developed a commercial version of the betatron with many improvements for reliable medical use, and in 1949 it installed the first unit at the University of Illinois College of Medicine. Its use in high-energy x-ray treatment commenced in 1950, and its use in electron-beam treatment in the 6–22-MeV range began the following year.[13] Workers at this facility and at a similar one at the Saskatoon Cancer Clinic in Canada developed many aspects of the basic radiological physics for the therapeutic use of high-energy electrons and x rays.[14,15]

During World War II, there was considerable development of high-frequency rf power oscillators at Stanford University and in England, and by 1948 microwave medical linear accelerators had been designed. An 8-MeV unit was installed in 1952 at the Hammersmith Hospital near London, followed by a 4-MeV unit at Newcastle-upon-Tyne in 1953 and a 6-MeV clinical unit at Stanford in 1956. By 1982, in the United States alone, hospitals were using approximately 700 linear accelerators and 35 betatrons for cancer treatment.

As a consequence of the development of electron accelerators, particularly the betatron and the linear accelerator, the physical potential for optimum radiation treatment with high-energy x rays and electrons came into being in the decade following World War II. This provided a challenge to the conventional radiation therapy procedures in the orthovoltage range (200–400 kilovolts, peak): No longer could local reddening of the skin be a treatment guide because the maximum deposition of energy now occurred far below the surface for deep-seated lesions. With



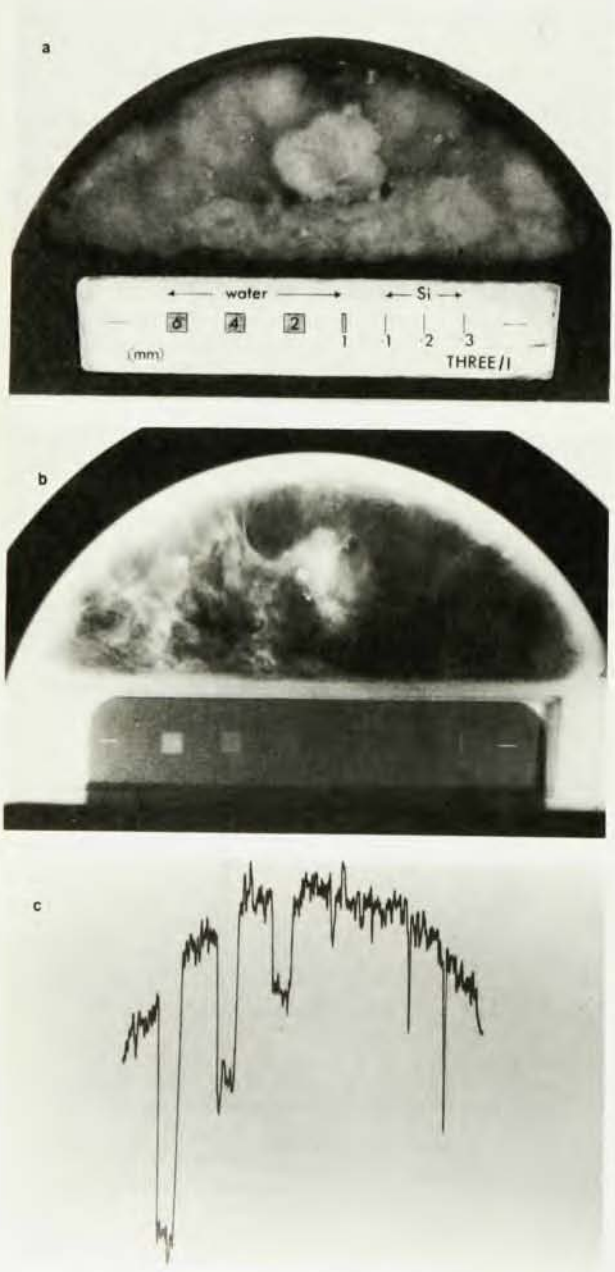
Mammographic surface exposure at 27 radiology departments involved in a project sponsored by the National Cancer Institute. The Regional Centers for Radiological Physics made these measurements over a three-year period. Substantial decrease in exposure was obtained on the basis of the measurement program. Figure 3

the ability to concentrate the radiation dose came the responsibility and necessity to locate the target region as accurately as possible, to plan the treatment in three dimensions, and to deliver the treatment precisely. Dosimetry problems far more difficult than those of orthovoltage x rays had to be solved, particularly for the use of electrons.

The use of cobalt-60 was advocated for several years for both externally and internally administered radiation treatment.[16] In 1946, William V. Mayneord, chairman of the physics department of the Royal Cancer Hospital in London, brought three discs of cobalt-59 to Canada for irradiation in the neutron reactor at Chalk River. The three resulting cobalt-60 sources were sent for testing to Harold E. Johns in Saskatoon, Ivan Smith in London, Ontario, and Gilbert Fletcher at the M. D. Anderson Hospital in Houston. Clinical deployment of teletherapy units containing cobalt-60 sources began[17] in 1951.

Dosimetry. The calculation or measurement of the energy deposited per unit mass of tissue for x rays, electrons and heavier particles has occupied the attention of many radiological physicists during much of the past half century, and the ensuing published literature can undoubtedly be measured in tons.

Most radiation users since Roentgen have used the ionization method of dosimetry, which remains the most widely used method to date. The fundamental work of Louis H. Gray of Cambridge relates ionization in a gaseous cavity to the energy deposited in the immediately surrounding wall or medium. The calculations require knowledge of the atomic constituents of the gas and wall, the energy spectrum of the secondary electrons, the average energy deposited per ion collected and the stopping power of the gas and wall as a function of energy. The "Bragg–Gray" law, with refinements in different applications, remains fundamental to dosimetry based on ionization. Ionization chambers have been designed with collection parameters that suit them for use in x-ray therapy; some have been designed for diagnostic energies (figures 3 and 4), some for electrons, and so on. The unit of absorbed dose is the Gray. One Gray is 10^4 ergs/gram, or 100 rads.



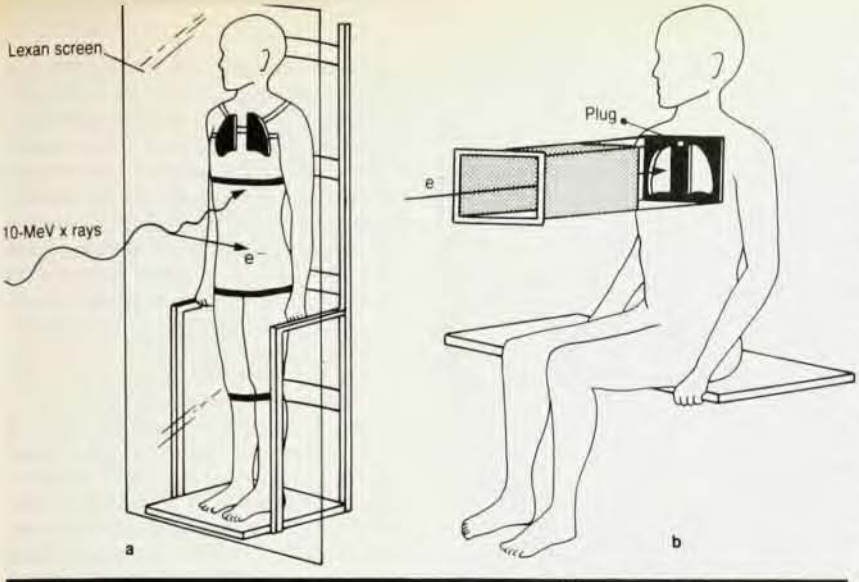
"Phantom" for representing a human breast with carcinoma. Tissue-equivalent material is employed together with an actual excised lesion (**a**). A physics "test strip" is embedded in the material. This unit permits physicists and radiologists to compare radiographs (such as **b**) made with different techniques. The microdensitometer trace (**c**) of a radiographic image of the test objects shows contrast and resolution. Figure 4

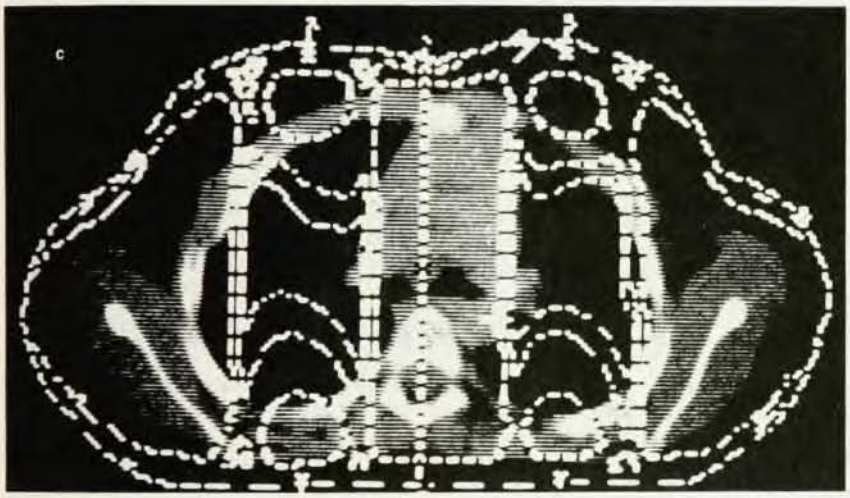
The Fricke ferrous sulfate dosimeter gives accurate results also. It uses ultraviolet light to measure the amount of ferric ion produced by the oxidation of ferrous ions during irradiation. Although ferrous sulfate can be used in different configurations and has essentially the same density and absorption characteristics as water, it has a relatively low sensitivity, requiring doses of a few thousand rads. Upon the recommendation of the American Association of Physicists in Medicine, the National Bureau of Standards commenced in 1967 a very helpful intercomparison service to electron-beam users based on mailed vials of ferrous sulfate.

The absorbed-dose calorimeter provides a sensitive and accurate basic calibration system. The technique, which my colleagues and I deveoped at Memorial Sloan-Kettering Cancer Center in the mid-1950s, involves a thermally isolated wafer surrounded by a homogeneous absorbing medium, both of whose temperatures are monitored with thermistors that are part of a bridge. The unit is calibrated electrically by passage of a known current through the wafer. Units are fabricated of carbon and of polystyrene for calibration of x-ray and electron beams. A unit constructed of a tissue equivalent containing adequate hydrogen has operated in the field for several years calibrating proton and neutron beams.

Other technologies employing diodes, radiographic film or the thermoluminescence of lithium fluoride or calcium fluoride are used widely and successfully as secondary methods.

Radiation treatment planning is vital to the exploitation of the high dose concentrations that are possible with megavolt x rays and electrons and with advanced internal sources. To achieve a tumoricidal dose and yet avoid irreparable damage to unavoidably irra-





Irradiation strategy intended to minimize exposure of the lungs of patients undergoing total-body irradiation prior to bone marrow transfusion. **(a)** Patient, with lungs protected by anterior and posterior lead blocks, is exposed to megavolt x rays. **(b)** Electron radiation exposes the anterior and posterior regions surrounding the lungs. **(c)** Isodose contours on a cross-sectional map show reduced lung dose after irradiation with both megavolt x rays and electrons. (Courtesy of G. J. Kutcher, Memorial Sloan-Kettering.) Figure 5

diated healthy tissue, the radiation therapist must achieve a specified tumor dose within narrow limits of uncertainty for a given treatment time. Therapists who design controlled clinical studies usually require that the specified tumor dose be achieved within 5%. Many steps in the treatment process can affect achievement of a given tumor dose, including

- the accuracy of calibration of the therapy department's basic dosimeter
- the accuracy of its use in calibrating the output of the radiation source at all of its energies, field sizes, angulations and distances
- the completeness and accuracy of the measurement of the three-dimensional distribution of dose in a relevant medium
- the completeness and accuracy of treatment planning
- the accuracy with which the treatment is delivered.

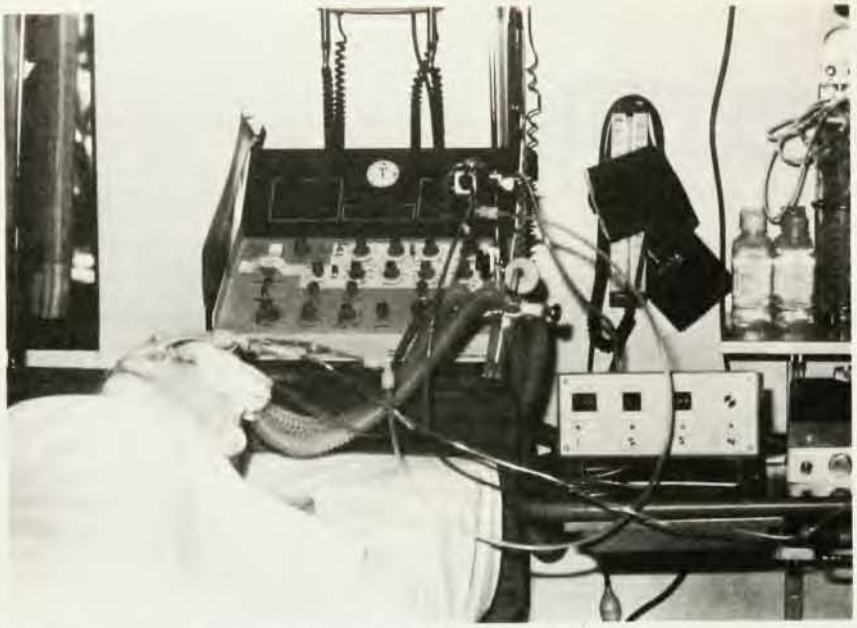
Failure to accomodate inhomogeneities adequately in treatment planning may affect the actual tumor dose substantially; an error in delivering any beam of radiation on any day of therapy may negate care in the rest of the sequence of treatments. The therapy plan may require modification during treatment if check-up examinations reveal changes in the configuration of the tumor or its surrounding tissue.

Radiation therapists need accurate three-dimensional information on the anatomy of the patient in the region to be irradiated. They obtained this from radiography and tomography originally, with an increasing contribution from ultrasonography and diagnostic nuclear-medicine scans. During the last decade, computed tomography has increasingly contributed such information for many patients. Those who plan treatment look forward to the availability of nuclear magnetic resonance imaging, in which the data are obtained initially on a three-dimensional basis. We should note that the density distributions in a computed tomography scan are obtained with x rays of much lower energy than those employed in therapy. To plan therapy, it is necessary to convert the CT numbers to those that are proportional to electron densities (figure 2).

With knowledge of the contours of the patient in the plane of the beam, one can design compensators to accomodate surface irregularities. One can tilt the plane of the customary flat isodose contours by designing attenuation wedges for the beam or bolusing material to place near the surface of the patient. Bolus is flexible material with x-ray attenuation properties similar to tissue. The design of compensators and wedges, together with the number of beams employed and their size, shape, weighting, energy and angle, determine the pattern of local energy deposition in the complex structure of the various tissues of the patient. Controlling such patterns requires not only accurate data, but automatic computation technology with highly specialized software.

Other techniques. In addition to the regular techniques used in radiation treatment, many specialized and experimental procedures involving radiation physics are under study. For instance, in some cases of leukemia, mostly in children, in which bone marrow transplantation is prescribed, total body irradiation is necessary to help avoid a graft-versus-host reaction. Many of the patients treated with total body doses of the order of 1000 rads develop interstitial pneumonitis, which is usually fatal. This has been countered in two ways: reduction of dose to the lungs while maintaining a high total body dose, and fractionating the total dose over time. Reduction of the lung dose is accomplished by designing lead shields for each individual patient to attenuate the x rays from the linear accelerator to the extent that the lung dose is about half of the prescribed midline pelvic dose. The tissue regions anterior and posterior to the lung, which contain some of the target hematopoietic blood cells that might contribute to the graft-versus-host reaction, are then irradiated by electrons both anteriorally and posteriorally. The complementary use of electrons and photons makes it possible to provide adequate total body irradiation with reduced dose to lung tissue (figure 5).

In addition, there is evidence that lung cells have a single-dose survival curve with a broad shoulder indicative of substantial repair following sublethal exposure, whereas both the normal and leukemic components of the hematopoietic system have a narrow



High-frequency jet ventilation system is an example of medical physics engineering. This system provides low-volume breaths to the patient at rates of 60–999 breaths/minute. The small white cabinet to the right of the patient is the electronic controller, which activates a high-speed solenoid valve that gates a blended air–oxygen mixture into the patient's upper airway via a specially designed humidifying injector. The high-velocity gases exiting the injector entrain additional gases from the conventional mechanical ventilator at the head of the patient's bed. There are a variety of alarm and monitoring functions. The system avoids excessively high and damaging peak airway pressures. Certain pathological pulmonary conditions that are unmanageable using conventional mechanical ventilation are manageable with this system. (Courtesy Saul Miodownik, Memorial Sloan-Kettering.) Figure 6

shoulder, if any, on their single-dose survival curves. Thus, fractionation of the dose accentuates the therapeutic ratio between the target cells of the hematopoietic system and those of the lungs. Survival of children undergoing total body irradiation increased remarkably with introduction of this system.

Other specialized techniques include intraoperative treatment, in which the lesion is irradiated while exposed during surgery, and hyperthermia, the use of elevated temperatures in addition to radiation.

A final example is the use of fast neutrons and other heavy particles for direct irradiation of cancer. The first neutron therapy was at the University of California in 1936, where researchers produced a beam of neutrons by accelerating deuterons in the cyclotron to 16 MeV and directing them at a beryllium target. John Lawrence, Ernest's brother and a clinical scientist at the University of California, used the neutrons in biological studies, primarily on the survival of rodents, while physicist Paul Aebersold intensively investigated the collimation of the neutrons. Robert Stone, a physician at the University of California, undertook clinical trials with the neutron beam following the dosimetry base established by Lawrence's biological studies. During the period from 1937 to 1943, 226 patients were treated with a fractionated schedule. Stone decided, in view of the severe late effect, that neutrons were not suitable for radiation therapy.

Subsequently, Gray advocated a reinvestigation of the role of neutron therapy. He had discovered the "oxygen effect," in which the level of a cell's oxygenation affected its sensitivity to x rays. Accordingly, the effect of neutrons should be more uniform. Further, studies carried out by radiobiologist Jack Fowler demonstrated that with neutrons there was substantially less repair between fractions than with x rays, making the biological effects of neutron doses more additive. Gray and Fowler thus suggested that Stone's total doses may have been too high. Several medical centers in various countries are now conducting clinical trials with cyclotron neutron beams.

The macrodose distribution (the spatial distribution of radiation energy absorbed per unit mass) of neutrons is not comparable to that achievable with high-energy x rays or high-energy electrons. The attractiveness of neutrons stems from their lack of dependence on the level of cell oxygenation and the hope that their use would result in decreased recurrence. Protons, negative pi mesons, and heavier nuclei are also undergoing clinical trials. Doctors at the University of California and at the Massachusetts General Hospital in Boston are using protons, primarily for pituitary irradiation and for superficial head and neck lesions. This work[18] makes use of the superior macrodose distribution properties of protons and pions and involves highly advanced treatment planning. A group at the Swiss Institute of Nuclear Research in Villigen, Switzerland, is doing a clinical study of negative pion irradiation. To focus pions, Stanford University's physics department designed a system that directs 60 pion beams at a single center. Electrons or protons strike a target, producing negative pions, which cryogenic magnets focus in 60 channels into the patient. The Swiss laboratory built a similar system, the "piotron," in 1979 for use with the synchrocyclotron at Villigen, which accelerates protons to energies up to 600 MeV. The first patient was treated in November 1980, and several have been treated since.

The use of cyclotron neutrons and other heavy particles is still in a research stage. For the immediately forseeable future, megavolt x rays and electrons will continue as the preferred radiation in view of the very good macrodose distributions and clinical results that they give.

Physics in nuclear medicine

Following the discovery of artificial radioactivity by Joliot and Irene Curie in Paris in 1934, Hevesy, who had already suggested using natural radionuclides as indicators of the distribution of elements when he was with Rutherford, studied the distribution of injected phosphorus-32 in various organs of the rat, and deduced its continuous turnover in the skeleton. In 1936 John Lawrence carried out the first injection of a radioactive isotope in a patient for therapeutic purpose with administration of phosphorus-32 to a patient with chronic lymphatic leukemia. Shortly after that, he administered phosphorous-32 to a patient to treat polycythemia vera, a blood disease in which red cells proliferate excessively. At the same time, his colleague Joseph Hamilton was carrying out pioneer experiments with radioactive sodium in patients and in normal human subjects. In the early 1940s, doctors began treating patients with thyroid cancer by taking advantage of the concentration of radioactive iodine-130 and iodine-131 in functioning metastatic lesions.

In the mid 1950s, Rosalyn Yalow and Solomon Berson developed the radioimmunoassay procedure for insulin, based on the principle of competitive binding by antibodies of natural and labeled hormones. This method is the basis of an increasing number of assays in diagnostic and physiological research and is used in hospitals throughout the

world. (See her article in PHYSICS TODAY, October 1979, page 25.) Yalow, a nuclear physicist, received the Nobel Prize for Medicine in 1977 in recognition of her contribution.

From 1951 to the present there have been major instrumental developments with respect to rectilinear scanning, gamma cameras, single-photon emission tomography and positron emission tomography. The next article in this issue describes these developments in medical imaging.

Although cyclotron-produced radionuclides were used for biomedical research almost from the time of the operation of the first cyclotrons, and although Ernest Lawrence dedicated his 60-inch unit as a medical cyclotron, such use was not general. The British Medical Research Council's authorization for the establishment of a cyclotron at the Hammersmith Hospital, in accordance with a program proposed by Gray, was an early recognition of the need for devoting a cyclotron exclusively to biomedical use. This machine has been used extensively for pioneer research in the production of a large number of radionuclides for medical use, including radioactive gases for pulmonary studies.

The next cyclotron exclusively for medical use was installed in 1965 in a hospital at the Washington University School of Medicine by Michel Ter-Pogossian, who is shown in figure 1. This machine is also of conventional design and was built by Allis-Chalmers. It is capable of accelerating deuterons to 8 MeV, and it has been used extensively for research on short-lived radionuclides, with particular emphasis on oxygen-15 and carbon-11, employed as labels for biologically significant compounds. Another Allis-Chalmers cyclotron was installed in 1967 at the Massachusetts General Hospital, where physicist Gordon Brownell uses it to produce positron emitters for his metabolic studies. Also in 1967, I installed a cyclotron at the Memorial Sloan-Kettering Cancer Center. This prototype unit, designed and built by The Cyclotron Corporation, is isochronous because of an azimuthally varying field, and it accelerates helium-3 ions as well as protons, deuterons and helium-4 ions. We had sought an isochronous unit to have the versatility for radionuclide production afforded by different nuclear reactions as well as the higher cross-sections available with helium-3, which it accelerates to over 23 MeV.

The use of a variety of biologically significant compounds labelled with cyclotron-produced radionuclides of oxygen, carbon and nitrogen—the elements commonly involved in human metabolic processes—is becoming important in the non-invasive study of organ and tumor function. L-glutamate labeled with nitrogen-13 is useful in visualizing a number of human tumors. In patients with bone tumors, changes in nitrogen-13 L-glutamate scans during chemotherapy are useful in the evaluation of the response of solid tumors to chemotherapy. Scans of patients and volunteers using other amino acids labeled with nitrogen-13, such as valine or leucine, indicate the utility of these compounds in studies of metabolic processes in the liver, myocardium and pancreas. Red blood cells, labeled with carbon-11 monoxide via inhalation of the radioactive gas have been used to assess changes in tumor vascularity following radiation therapy. Alpha-aminoisobutyric acid, a non-metabolized amino acid, has been successfully labeled with carbon-11, and its distribution in patients indicates it may be useful for metabolic studies. Fluorodeoxyglucose is being used[19] in the study of cerebral and myocardial function. Celebral studies are also being carried out with molecular oxygen-15 and with water or carbon monoxide labelled with oxygen-15. Cardiac studies are using[20] carbon-11 palmitate, oxgyen-15 water and oxygen-15 carbon monoxide.

Imaging with nmr. Medical physicists have been active in the development of imaging techniques in diagnostic radiology, as well as in the development of quality-assurance procedures. Some of these imaging techniques include digital subtraction angiography, x-ray tomography, ultrasound imaging, xeroradiography, computed axial tomography and nuclear magnetic resonance. In the case of ultrasound, it is interesting that the transducer is based on the piezoelectric effect, discovered[21] by Jacques and Pierre Curie in 1880.

Nuclear magnetic resonance imaging currently is generating much excitement in the medical imaging community. Because the rf photon energies used are much lower than those of x rays—about 10^{-7} eV versus about 10^{6} eV—nmr imaging promises more information at less risk to the patient. Unlike ionizing radiation, the rf electromagnetic field detected in nmr contains information about molecular bonds but does not have enough energy to break them. As far as is known, the radiofrequency intensities and the magnetic field strengths used at the present time are not hazardous. Currently, imaging is done almost entirely with hydrogen, this being both the most abundant element in the body and the most sensitive to nmr.

We have seen that radiation physics has made important contributions to solving biomedical problems in medical institutions. As further research and applications extend the benefits of ionizing as well as non-ionizing radiation, the need to continue the highly productive alliance of physics and medicine will increase.

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