NUCLEAR PHYSICS IN MEDICINE

Radioisotopes now vie with x rays as tools for diagnosis and treatment; high-energy beams, neutrons and pions are also becoming important for radiation therapy.

Gordon L. Brownell and Robert J. Shalek

RADIATION THERAPY and radioisotope imaging have become as common to modern medicine as stethoscopes and hypodermic needles. They illustrate the impact that nuclear physics has had upon medical diagnosis and therapy. For example, the design of particle accelerators led to radiation treatment with increasingly higher energies. Nuclear reactors provided a wide variety of radioisotopes for nuclear medicine. Development of instruments such as the Anger camera have improved imaging techniques. At times, nuclear physicists themselves have decided to apply their skills to health-related areas, and an increasing number of young physicists are now entering this field.

Among the many fields that combine the physical sciences and the medical arts, medical physics is the one that most nearly encompasses the application of nuclear physics to medical diagnosis and therapy. Of the three areas of medical physics oriented toward nuclear physics—radiation therapy, nuclear medicine and diagnostic radiology—we will discuss here only the first two. Diagnostic x-ray methods have been improved with the advent of better machines, image intensifiers and contrast media, and there are many physical problems in this area, such as the possibility of neutron radiography.

The intermingling of the physical and biological sciences is by no means new. Leonardo da Vinci made significant contributions to physics, engineering and physiology, and Benjamin Franklin made remarkable observations in physics and medicine. Perhaps the renewed interest in these interface fields denotes a return to a more catholic view of science and engineering.

The discovery of x rays in 1895 by Wilhelm K. Roentgen and radium, shortly thereafter, by Marie Curie initiated the applied arts of radiation diagnosis and therapy. Shortly after these discoveries, medical applications were made—first in diagnostic radiology and then in therapeutic use. Within seven months, a medical roentgen-ray journal was being published in the UK. This chain of events perhaps still holds a record for the shortest time between a scientific discovery and the appearance of a journal devoted to that subject.

Radium has a similar history of rapid application to the healing arts. Discovered in 1898 by the Curies, radium was in use by 1900. A physician friend of the Curies treated skin lesions with it. An American physician, Robert Abbey, reported in 1913 the first cure of carcinoma of the cervix which had been treated with radium seven years earlier.

NUCLEAR MEDICINE

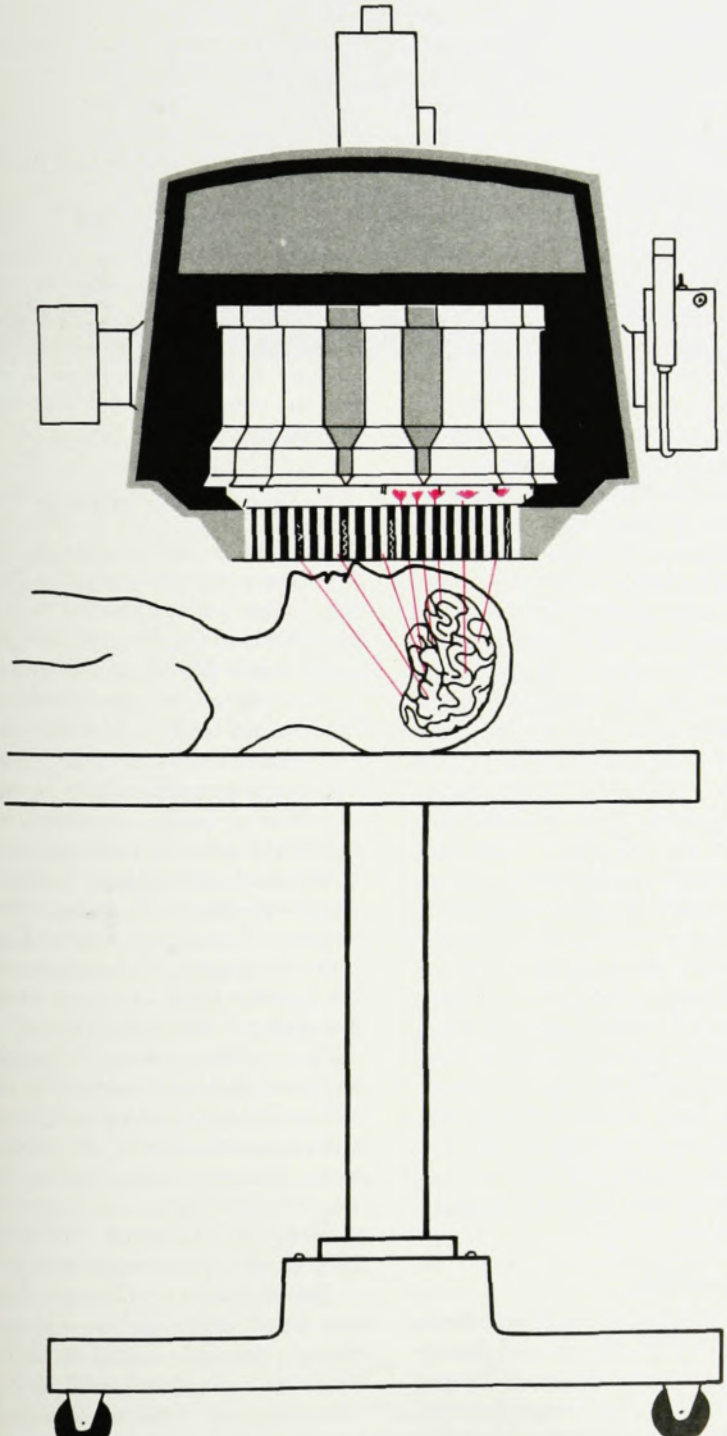
More recently, artificially produced radioisotopes are becoming important in diagnosis and treatment of disease and promise to compete with x rays as a tool in diagnosis. Nuclear medicine is the field that is generally concerned with the use of these radioisotopes. Its origin is difficult to pinpoint, but important dates would include the discovery of natural radioactivity by Antoine H. Becquerel in 1896, the invention of the cyclotron by Ernest O. Lawrence in 1931 and the development of the nuclear reactor in the early 1940's. Although each of these physical developments was followed closely by biological and medical applications, the principal impetus to nuclear medicine has been the nuclear reactor, which has made available large quantities of radioactive isotopes.

Today, the importance of nuclear medicine is illustrated by a survey conducted by the Stanford Research Institute (SRI) for the National Center for Radiological Health of the Department of Health, Education and Welfare. They found that US hospitals performed approximately 400 000 administrations of radioisotopes to patients for imaging procedures, over 300 000 studies of biological functions *in vivo*, and over 700 000 *in vitro* studies during 1966. An estimate of the annual growth rate of nuclear medicine was approximately 15% per year. Testifying to this growth are the existence of nuclear-medicine sections in many hospitals and establishment of independent departments of nuclear medicine in medical schools.

The statistics of nuclear medicine, however, do not give the complete picture of the growing importance of this field. Many procedures now commonly performed in nuclear-medicine laboratories have been refined so that they have become the procedure of choice in the diagnosis of certain diseases. For example, many medical groups feel that radioisotope brain imaging is the single most useful test for the diagnosis and localization of brain tumors. Radioisotope imaging has become nearly indispensable for the diagnosis of abnormalities in thyroid, lung, kidney, liver, and bone.

Nuclear medicine may generally be divided into the three areas cited in the SRI survey. One of these is the study of biological functions within the patient. A classical technique is the determination of thyroid activity by measuring the uptake of a radioisotope of iodine, I^{131}. Another area is the development of techniques for

ANGER CAMERA forms image of portion of brain. Gamma rays (color) from radioisotopes pass through collimators to scintillator. Photomultiplier tubes detect signals, which are processed and displayed by computer. —FIG. 1



visualizing organs or abnormalities. Recently the imaging of isotopes within a patient has developed rapidly as a result of improvements in isotope techniques and instrumentation. It is in this area that nuclear medicine has made its greatest contribution to the diagnosis of patients. Finally, nuclear medicine includes *in vitro* (test-tube) studies designed to determine properties of samples taken from patients. For example, the thyroid function is determined by observation of the absorption of I^{125}—or I^{131}—labelled triiodiothyronine in human red-blood cells.

Imaging devices

The instrumentation in nuclear medicine has seen rapid development in the past several years, particularly in the area of radioisotope imaging. Moving scanners, that is, detectors that move over the region of interest, are rapidly giving way to stationary cameras. One of the most widely used imaging devices at the present time is the Anger camera developed by Hal Anger of the Donner Laboratories at the University of California at Berkeley. This device, sketched in figure 1, employs a thin, large-area sodium-iodide scintillator backed by 19 photomultiplier tubes. High quality images are obtained in seconds if sufficient activity is available.

Gamma rays from the area under study pass through a collimator into the scintillator. The distribution of light among the phototubes indicates the location of the interaction. One picture, composed of approximately 100 000 such interactions, may be displayed on an oscilloscope and recorded with a Polaroid camera.

More and more imaging devices are using computer interfaces to extend and improve the output information. For example, the computer may assemble pictures from different views in a way that emphasizes different planes. This technique of tomography (a term borrowed from x-ray studies) results in a three-dimensional picture of the object under study.

Computers and analog devices can also improve the image by correcting for the finite resolution introduced by the collimators and by smoothing the fluctuations caused by low statistics. Visualization can be improved either by translating intensity to color (black and white images are limited by the finite range of grey shades) or by using volumetric techniques to make two-dimensional images appear three dimensional. A volumetric display of a brain imaged by the Hybrid Positron Scanner (figure 2) is shown in figure 3. Finally, by recording activity over a period of time, the computer can extract and display dynamic quantities.

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Production of new isotopes

Radioisotopes in nuclear medicine have seen equally spectacular development. The most widely used isotope at the present time, Tc^{99*}, was essentially unknown five years ago. This isotope was developed at Brookhaven National Laboratories and its medical applications were pioneered at the Argonne Cancer Hospital. One of a series of mother–daughter pairs that are coming into prominence in nuclear medicine, it has the advantages of the shelf life of the 66-hour Mo^{99} parent, together with the lowered radiation dose of the 6-hour Tc^{99*} daughter. The isotope Tc^{99*} gives rise to a 140-keV gamma ray. The lack of beta radiation results in a markedly decreased radiation dose to the patient and the low-energy gamma ray permits finer collimators to be used.

At the present time, cyclotrons, typically capable of producing 6- or 8-MeV deuterons, have been or are in the process of being installed at the Massachusetts General Hospital in Boston, Sloan Kettering Institute in New York, Washington University in St Louis, Mt Sinai Hospital in Miami, Argonne Cancer Hospital in Chicago, and the University of California at Los Angeles. Among the applications of these machines is the production of the three short-lived isotopes, O^{15}, N^{13} and C^{11}, having half lives of 2, 10 and 20 minutes. Michael Ter-Pogossian at Washington University in St Louis and a group at the Hammersmith Hospital in London under Jack Fowler did the pioneering work with these isotopes. Besides their application in pulmonary physiology, these three short-lived isotopes have direct application to measurement of blood flow and oxygen utilization in most tissues of the body, including brain, heart muscle, liver and kidney. They should be particularly valuable in following the status of transplants. The isotope C^{11} offers many possibilities, as yet largely unexplored, for *in vivo* studies of the fate of labelled organic materials.

Positron emitters

With the advent of small cyclotrons we see an increased interest in the application of positron-emitting isotopes and in the use of coincidence detection of the annihilation radiation for radioisotope imaging. Lead collimation is not required, so higher sensitivities can, at least in principle, be obtained. Also, as attenuation is constant through the object, absolute measurements can be made conveniently by external standards. High-resolution images of positron-emitting radioisotopes such as F^{18} in bone have been obtained from the Anger camera in a positron mode.

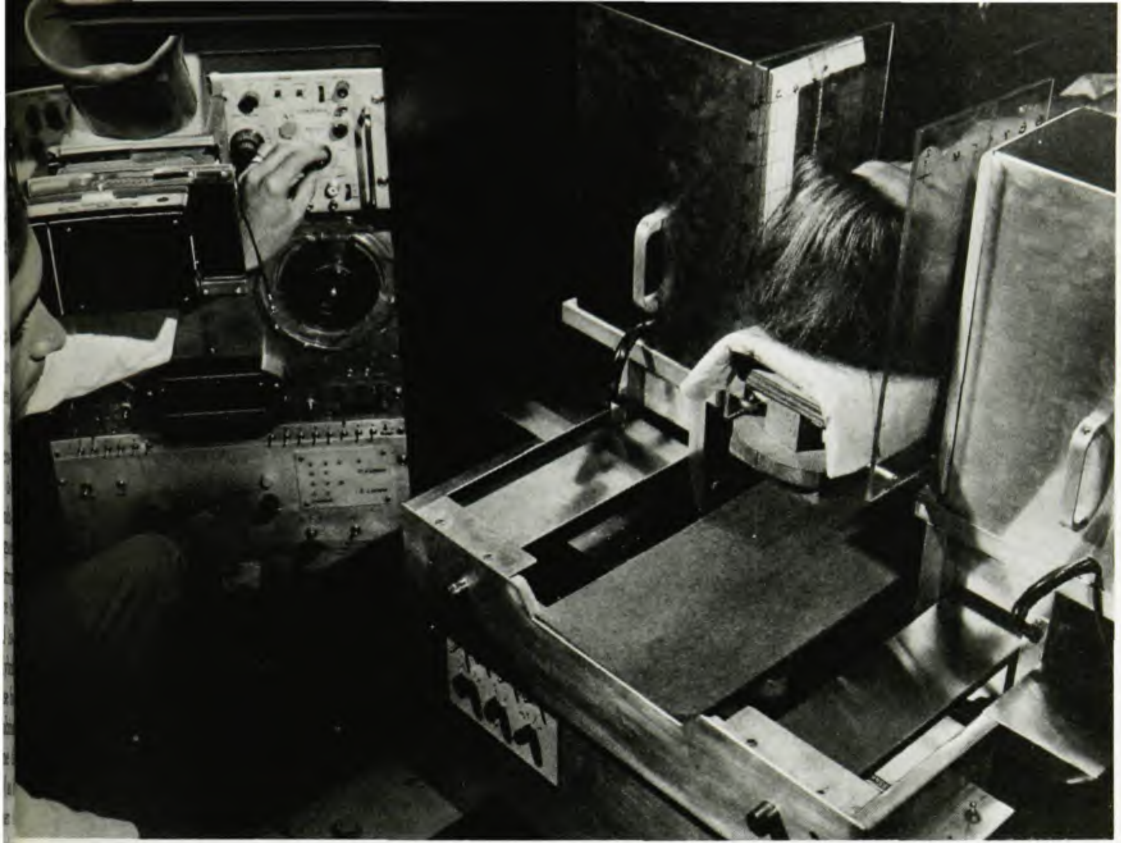
A series of positron devices capable of high data-collection rates are being developed at the Massachusetts General Hospital (MGH). One of these, the MGH positron camera, consists of two banks, with 127 detectors each, which record the annihilation pairs. The circuitry is designed eventually to handle 10^5 positron events per sec and may therefore be used with the safer, short-lived isotopes. A second device, the Hybrid Positron Scanner, is in routine use for brain-tumor localization. It combines the features of a scanner in one direction and multiple detectors (as in the Anger camera) in the other direction. It is shown in figure 2, alongside the coincidence and data-recording system.

RADIATION THERAPY

One human in eight dies from cancer; the disease may be known to the patient for only a few months or it may have persisted for thirty or more years. It is a subtle disease in the sense that cancer cells are not greatly different from normal cells. Probably cancer cells arise from normal cells by mutation, and this mutation may be caused by a variety of agents, including ultraviolet light, ionizing radiation, viruses, or chemical carcinogens. Clinically, cancer appears to be many different diseases. The major forms of treatment are surgery and radiation, with a few specific types of cancer that are amenable to chemical treatment.

The course of events following radiation of biological material is partly known. The physical interactions are well understood, and the biological consequences, whether death, mutation, or other effects, are quantitatively measured; however, the intermediate events are unknown to a greater or lesser extent. Despite a large amount of study, radiation therapists still rely primarily on the clinical experience gained through trial and error. Therapists are slow to change from tested methods.

Of all cases of cancer, about half respond well to radiation. About one-



HYBRID POSITRON SCANNER is combination of a moving scanner and a stationary camera. Patient places head between two banks of detectors (right), which then move along one axis. Electronics is shown on left. The data is processed by computer to produce images like those shown in figure 3. —FIG. 2

fourth are treated by radiation alone, and one-fourth are treated by radiation and surgery, or by radiation and chemotherapy. Although radiation therapy proceeds primarily on clinical experience, the latitude permitted the therapist is not wide: The difference between what is too little and what is too much radiation is not great. The proper amount depends upon a complexity of factors such as the size of the tumor, the type of tumor, the number of treatments and the total time of treatment. Thus, a technology has arisen that endeavors to deliver a prescribed absorbed dose of radiation with relatively high precision. The task of the physicist is to determine the amount of energy arriving at different parts of the body with a precision that is adequate for the physician—better than 5%. The varied shapes of people, the placement of bones, air cavities, lungs, and even the patient's change of shape during treatment must be considered.

Toward higher energies

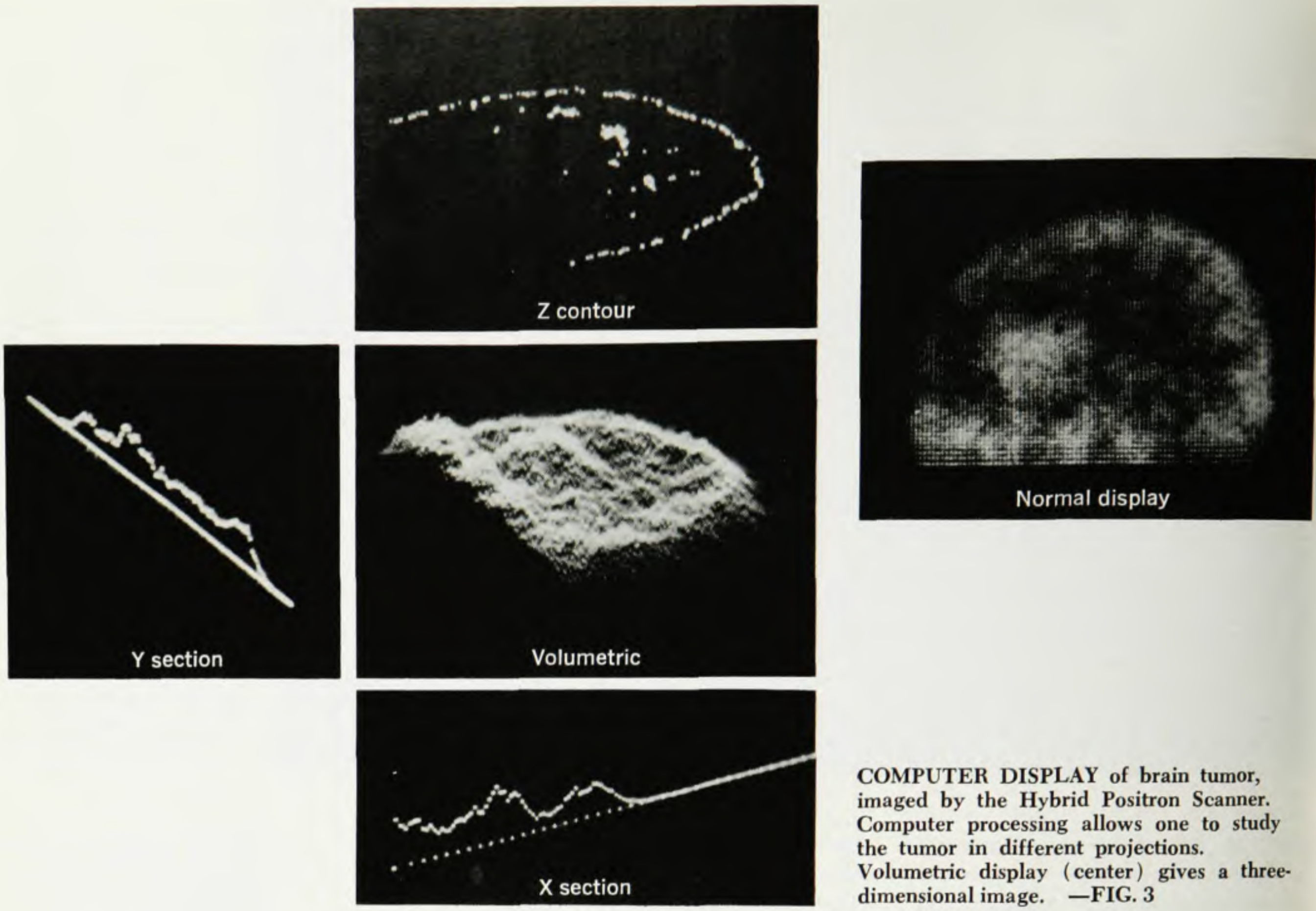
The period between the discovery of x rays and radium and about 1920 is not remembered by physicists who are now alive. However, during this period, Paul-Ulrich Villard, William Duane, Leo Szilard, W. Friedrich and others made significant contributions. The units of radiation measurement were beginning to be defined, and improvements were being made in apparatus and ways of delivering radiation. The modern era in physics related to radiation therapy began around 1920 with the contributions to measurements by G. Failla in the US and Rolf M. Sievert in Sweden. They were soon followed by Edith Quimby and Lauriston S. Taylor in the US and W. V. Mayneord, Louis Harold Gray, Herbert M. Parker and others in the UK.

From the late 1930's onward, discoveries in physics, particularly nuclear physics, have had an enormous impact upon radiation therapy. For the most part these contributions have consisted of improved machinery for the delivery of radiation. The invention of the electrostatic accelerator by Robert Van de Graaff, the discovery of cobalt 60 by Glenn T. Seaborg, the invention of the betatron by Donald Kerst, and the electron linear accelerator by R. Wideroe and William W. Hansen, have permitted radiation to be delivered in patterns that are much more favorable than by lower-energy x-ray machines. They provide more radiation to the tumor and less to healthy tissue.

These high-energy radiations have three physical advantages over those of lower energy. The first of these is the almost equal energy absorption per gram of muscle, bone and fat tissue. For lower-energy radiations, as for very much higher energies, these tissues absorb different amounts of energy for the same radiation exposure. For example, with 250-keV x rays, bone may absorb 25% more radiation than desirable. The treatment may be limited and the bone may in fact cast a shadow, preventing treatment of areas behind it. With cobalt-60 gamma rays, bone absorbs about 8% less radiation than muscle absorbs per gram and casts only a slight shadow beyond (due to its higher density).

A second advantage of the higher-energy radiation is the possibility of delivering higher radiation dose at depth, compared to the dose at maximum. For the treatment of thick portions of the body such as the trunk, this is usually an advantage. A third advantage is the existence of electron buildup, causing the maximal dose to occur beneath the surface of the skin. Thus for cobalt-60 radiation the maximum occurs at about a half-centimeter depth, and for 22-MeV betatron x rays the maximum occurs at about 4 cm. Because the maximum occurs beneath the skin, the tolerance of the skin to radiation is not then the limiting factor in treatment as it is for lower energies.

It is difficult to evaluate directly the improvement of treatment created by the high-energy machines. Between 1940 and 1960, cure rates of cancer by radiation therapy improved



COMPUTER DISPLAY of brain tumor, imaged by the Hybrid Positron Scanner. Computer processing allows one to study the tumor in different projections. Volumetric display (center) gives a three-dimensional image. —FIG. 3

dramatically, as shown in Table I. Some, but not all, of the credit for the increased five-year survival rates can be attributed to improved methods of delivery and calculation of radiation dose. Other factors, such as the improvement of application techniques, skill of the radiation therapist and earlier cancer detection are also responsible. Table I includes cases where surgery is used in conjunction with radiation, so that, in part, the improved skill of the surgeon has also contributed. But one can say that, in the 20-year period between 1940 and 1960, cure rates have improved by better than a factor of two.

The oxygen effect

Future contributions of nuclear physicists may result from exploiting the oxygen effect in radiation biology. The radiation sensitivity of cells is universally observed to be about two and a half times greater in the presence of oxygen than in its absence. Although several theories have been advanced to explain the oxygen effect, a description of the most widely accepted theory will give an idea of the type of mechanisms involved. Radiation causes the breakdown of important biological molecules, most probably freeing a hydrogen radical and also leaving a radical. If this hydrogen is returned to the molecule, the damage is repaired. However, the remaining radical is very likely to react with any molecular oxygen that is present, forming an organic peroxide. In this case the hydrogen is not returned and the biologically important molecules suffer irreversible damage.

Gray, a former nuclear physicist, realized the importance of this effect. Together with the knowledge that many solid tumors have regions of *low* oxygen supply, it provides the rationale for an improvement in therapy. A large scale effort over the world is under way to exploit this idea. The aim is to deliver enough radiation to the tumor to cause it to die but not so much that the normal tissue cannot recover.

Neutron therapy

The other approach is to use radiation with higher specific ionization, or linear energy transfer. One such effort, in progress at Hammersmith Hospital, involves fast neutrons. These neutrons, because of the higher specific ionization of the recoil protons and nuclei, cause irreversible damage by a mechanism that competes with the oxygen effect. Consequently the amount of irreversible damage is not as strongly dependent on the oxygen present; the sensitivity of oxygenated cells to radiation is only 50% greater than that of similar cells without oxygen.

Another possibility of neutron therapy is the application of californium 252 (a transuranic element discovered by Seaborg), which is a spontaneous neutron emitter. A yet bolder venture, the use of negative pions, has been pursued for a number of years by Chaim Richman of Dallas in collaboration with the Donner Laboratory at the University of California. Negative pions cause disintegration of light nuclei in a star, yielding various heavy particles, including alpha particles, protons and neutrons. Thus, at the tumor there is high specific ionization having a high biological effect for the energy absorbed and also a low oxygen effect. The region between the body surface and the tumor receives a low absorbed dose of lightly ionizing radiation with a low biological effect per unit of energy absorbed. The depth of the star can be controlled by

Table I. 5-Year Cancer Survival Rates* *

Region of cancer	*1940*	*1960*
Oral cavity	25–30%	50–60%
Oropharynx (base of tongue, tonsillar region, pharyngeal walls)	15%	30–40%
Nasopharynx	15%	35%
Supraglottic region of larynx	15–20%	50%
Pyriform sinus and hypopharynx	5–10%	30%
Squamous cell carcinoma of uterine cervix	25–30%	60%
Infiltrative tumors of urinary bladder (Stage B_2-C)	10–15%	30–35%

* *The 5-year survival rates are ranges of published results from institutions throughout the world (from G. H. Fletcher).*

varying the energy of the pion beam. In 1972 further biological experimentation and radiation therapy with pions will be possible with the Los Alamos Meson Physics Facility. Pion therapy is also planned in Canada and Switzerland.

INCREASED FUTURE ROLE?

Many of the present leaders in the field of medical physics originated from a few nuclear-physics centers. In particular, a group of graduate students and other collaborators working in nuclear physics with Donald Kerst at the University of Illinois in the 1940's include present leaders in medical physics, such as Gail Adams, Arnold Feldman, Lawrence Lanzl, John Laughlin, Jacques Ovadia and Lester Skaggs. Other groups worked under Robley Evans at the Massachusetts Institute of Technology, Ernest and John Lawrence at Berkeley, and Failla at Columbia.

We are currently seeing a wave of interest among graduate students and young investigators in nuclear physics towards medical and biological problems. This interest originates partly because of the current decrease in opportunities in nuclear physics, but perhaps more because of a marked desire among physicists of all types to contribute more directly towards the benefit of mankind.

To assess the magnitude of this trend, one might estimate the number of doctoral-level nuclear physicists who have migrated to medical and biological areas. Rough estimates of this kind, made by examining the composition of various medically-oriented scientific societies, such as The American Association of Physicists in Medicine (AAPM), indicate that the total number of doctoral-level nuclear physicists migrating to the health areas might be as high as several hundred. More precise figures should emerge from studies now being made by the AAPM under the direction of Lanzl and by the National Academy of Science.

It is equally difficult to project a number for future involvement of nuclear physicists in medicine. In general, most scientific societies in the biological area are growing at the rate of 10–15% per year. This could mean that between 50 to 100 doctoral-level nuclear physicists might be absorbed in the health areas per year. However, doctoral programs designed for medical physics and medical engineering are now emerging, and any such projection into the future should be made with a good deal of skepticism. Further, one might question the logic of preparing large numbers of individuals in nuclear physics if their aim is to enter health-related fields. The answer may lie in a relaxing of the rigid compartments of graduate-school training.

That nuclear physics has and will continue to make a significant contribution to biology and medicine is beyond question. As in the past, contributions will probably result both from basic findings in physics and from the conscious application of physics to medicine.

Bibliography

1. *Aspects of Medical Physics* (J. Rotblat, ed.), Taylor and Francis, London (1966).
2. *Instrumentation in Nuclear Medicine* (G. J. Hine, ed.), Academic, New York (1967).
3. *Principles of Nuclear Medicine* (H. N. Wagner Jr, ed.), Saunders, Philadelphia (1968).
4. "High-Energy Radiation Therapy Dosimetry" (J. S. Laughlin, consulting ed.) in Ann. N. Y. Acad. Sci. **161**, 1 (1969).
5. *Radiation Dosimetry (2nd ed.) I, II, III* (F. H. Attix, W. C. Roesch, E. Tochilin, eds.) Academic, New York (1966, 1968, 1969). □