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THE DEVELOPMENT OF NUCLEAR MEDICINE

by

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Oak Ridge, Tennessee

The impact of nuclear energy, both for war and peace, has been tremendous in all phases of human life. There is a growing realization that one of the greatest contributions is in nuclear medicine.

Nuclear medicine is a term evolved only in recent years to cover the wide variety of uses of nuclear energy in medicine. At present it need not be defined more exactly. Admittedly, many clinical uses are still developmental and nuclear medicine may not become a limited specialty in itself, but it is certain to continue to grow rapidly both in usage and scope.

Nuclear energy as here used is in the form of ionising radiation. This encompasses a variety of radiations and a broad range of energies.

In retrospect, radiation, whether from atomic nuclei or from machines, has had a revolutionary role in the development of all fields of science, including medicine. However, the early use of radioactive materials in medical and biological studies was limited. Prior to 1930, the only isotopes available were the naturally occurring forms which normally have very little presence in biological systems.

This limited the use of radioactive isotopes as tracer atoms in biological investigations and precluded their use in diagnostic and therapeutic applications which involve metabolism of the radiomaterial in the patient.

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Nuclear Transformation

A great impetus to the development of nuclear science was the discovery by Rutherford in 1919 that the structure of matter could be changed by bombarding elements with alpha particles from radium. He found when alpha particles from radium bombarded nitrogen, the nitrogen nuclei were transformed into nuclei of oxygen. Rutherford thus had achieved the first deliberate artificial transformation of an atomic nucleus.

During the 1920's, physical scientists using the principle of Rutherford's discovery continued studies of the mechanism of nuclear processes. They soon realized that radium as a source of subatomic projectiles had serious limitations. Only the alpha particles from radium were effective in nuclear transformation; the number of alpha particles was not sufficient for desirable experimentation; and the energy and penetration of alpha particles was severely limited.

In 1932, another valuable contribution to this field was made in England when Cockroft and Walton built a high voltage transformer type of accelerator capable of producing protons with sufficient energy to bring about a nuclear transformation. They converted two different isotopes of lithium to two different isotopes of helium and observed that during the conversion mass was converted into energy. This was the first device to convert mass to energy, though the amount released was infinitesimally small.

A great impetus to nuclear science came with E.O. Lawrence's invention of the cyclotron; it was the result of an idea conceived by him in 1929. He and his associates

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were able to demonstrate nuclear transformation in 1932 almost immediately following that by Cockroft and Walton. He and his associates at the University of California, Berkeley, built the first operating cyclotron late in 1930. This atom smasher, as it was then known, has proved to be the most useful and versatile man-made device for affecting nuclear transformations with accelerated high energy particles.

Another important contribution to nuclear science was Urey's discovery in 1932 of deuterium or heavy hydrogen. His discovery provided a new source of subatomic projectiles, deuterons (nuclei of deuterium), and made possible the labeling of water so that it could be used as a tracer in living systems.

Before the end of 1933, Lawrence and colleagues developed a cyclotron capable of yielding a beam of deuterons (heavy hydrogen nuclei) of 3 million electron volts (3 Mev) and with a radiation intensity equivalent to enormous quantities of radium. The cyclotron was able to accelerate protons, deuterons, and alpha particles.

It was also possible to produce a prolific stream of neutrons, the new subatomic particles identified by Chadwick in 1932, secondary to the bombardment of light materials with deuterons. It was little realized that neutrons would later prove to be the key to the release of atomic energy and a copious source of radioisotopes.

The usefulness of the cyclotron was enormously extended by the Joliots' discovery in 1934 of artificially induced radioactivity. Almost immediately it became an invaluable tool for inducing radioactivity.

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Availability of Radioisotopes

It was now possible for the first time to produce radioisotopes of nearly all elements in quantities sufficient to begin medical and biological research. This research, although limited, laid the groundwork for the later greatly expanded utilization of radiomaterials in medicine.

By the start of World War II, radioisotopes were being made in cyclotrons in many parts of the world. Again, however, the wide-scale use of radioisotopes was not possible. The cyclotron could produce only a limited supply of a very wide variety.

Because Europe became involved earlier in World War II than the United States, radioisotope production and utilization developed slower abroad in the late 1930's than in this country. However, many of the significant early developments leading to nuclear medicine were originated by scientists on the European continent.

It is interesting to note that from 1941 until 1946 the Massachusetts Institute of Technology cyclotron maintained essentially a 24-hour-per-day bombardment schedule producing radiophosphorus, radioiodine, and other isotopes for use in medical research and therapy throughout this country and Canada. This machine was kept operating to supply the needs of the country while other cyclotron laboratories were either depopulated or taken over for wartime research.

On December 2, 1942, Fermi and his co-workers at the University of Chicago achieved the first self-sustained chain reaction. From this monumental work

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has come the uranium nuclear reactor which has virtually eliminated availability as a major obstacle in radioisotope utilization. The nuclear reactor has proved to be an ideal production unit. Although not as wide a variety of radioisotopes can be produced in the reactor as in the cyclotron, what is much more important, the radioisotopes can be produced in larger quantities at much lower cost. With the reactor it is possible to produce many different radioisotopes concurrently. Radioisotopes of nearly all the elements can be produced in quantities thousands to a million times greater than in the cyclotron and other accelerators.

It is interesting that during the spring of 1945 the wartime reactor at the Clinton Laboratories, Oak Ridge, Tennessee, was producing radiophosphorus, but due to secrecy of the project, the material could not be distributed directly to would-be users. Instead the radiophosphorus was sent to the Berkeley cyclotron group which redistributed it. Though it could not be credited as such, this was actually the first public distribution of reactor-produced isotopes.

The first announcement of the availability of reactor radioisotopes for public distribution was published in the June 14, 1946, issue of SCIENCE. The first shipment, a small quantity of Carbon 14, was made to the Bernard Free Skin and Cancer Hospital in St. Louis, Missouri, on August 2, 1946.

Today, almost ten years after the Atomic Energy Commission first began public distribution of radioisotopes, over 1200 medical institutions in this country are using these materials. More than 50 countries have received radiomaterial

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from the United States since foreign distribution began in September 1949. Since 1946, several hundred thousand shipments have been made to radioisotope users from Commission facilities and commercial suppliers; over 80,000 of these shipments have been made by Oak Ridge National Laboratory.

Early History of Clinical Applications

Radioactivity was associated with medicine 35 years before the first application of an artificial radioisotope to a human subject. It was only five years after Becquerel's discovery in 1896 of the radioactive properties of uranium and three years after the Curies in 1898 identified radium and polonium that Danlos and Block in 1901 used radium to treat human disease. Radium therapy thus has now been developed over a 55-year period.

Over 20 years after Danlos and Block used radium therapeutically, the first application of radiomaterials as a biological tracer had its inception when Hevesy in 1923 used a naturally occurring isotope of lead (Pb-212-thorium-B) to study the absorption and translocation of that element in plants.

Hevesy and Hofer reported the first clinical study with stable isotopes in 1934 when they used deuterium to investigate the total water content and half life of water molecules in their own bodies. This is not only the first clinical application of isotopes as tracers but also the first application of the isotope dilution principle which has found such widespread use in clinical studies.

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Twelve years later, in the fall of 1935, an artificially produced radioisotope was first applied to a biological problem when Chiewitz and Hevesy used radioactive phosphorus as a tracer to investigate the distribution and excretion of that element in rats.

Less than a year later on March 23, 1936, Hamilton and Stone in California employed the first artificially produced radioisotope to a clinical problem when they used cyclotron produced sodium in the investigation of the uptake and excretion of that element in three patients with leukemia and allied diseases.

On Christmas Eve of 1936, J. H. Lawrence and his associates initiated the use of artificial radioisotopes in therapy by using radiophosphorus for the treatment of leukemia. The first successful therapy, however, did not begin until 1938 when Lawrence treated a series of leukemia and polycythemia patients. Since that time radiophosphorus has proved to be the choice of many clinics for the therapy of polycythemia vera and chronic leukemia.

The thyroid gland's unique characteristic to accumulate iodine selectively in relatively high concentration was known long before the radioisotope era. It is not surprising that thyroid physiologists recognized early the potentialities of radioiodine as a research tool.

In 1938, soon after learning from Karl Compton that Fermi and his Italian coworkers had prepared radioactive isotopes of iodine, Herts, Roberts, and Evans in Boston initiated the use of radioiodine in animal studies. They were able

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to demonstrate with a Geiger-Mueller counter the selectivity and rapidity by which radioiodine was taken up by the thyroid gland.

Hamilton and Soley in 1939 reported thyroid uptake studies in patients using radioiodine which substantiated the results obtained by Herts and his associates from their animal studies.

About the same time radioiodine tracer studies were carried out by Leblond and Sue in France.

The therapeutic use of radioiodine for the treatment of hyperthyroidism was reported for the first time simultaneously in 1942 by Herts and Roberts, and Hamilton and Lawrence.

The ability of metastatic carcinoma of the thyroid gland to accumulate radioiodine was reported by Keston, Ball, Frantz, and Palmer in 1942. Later studies, reported by Marinelli, Foote, Hill, and Hocker in 1947, showed that only certain types of thyroid cancers will accumulate radioiodine.

Currently, because of the thyroid gland's ability to concentrate radioiodine and the results of pioneer studies, many physicians believe radioiodine the best mode of therapy for hyperthyroidism, and it has received almost universal acceptance as an aid in diagnosis of thyroid disease.

All of the early hopes for radioiodine in the treatment of carcinoma of the thyroid have not materialized. It has been found that in order to obtain

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beneficial response from radioiodine the cancer cell must have an affinity for iodine similar to that of a normal cell.

Prior to the nuclear reactor, the medical use of artificially produced radioisotopes developed slowly, primarily because few groups had sufficient quantities of radiomaterials, necessary knowledge, facilities and techniques to carry out extensive research programs.

With the tremendous wartime drive to attain the release of atomic energy through the nuclear chain reaction, there began a scientific team effort unparalleled in history. This team effort not only achieved its primary goal but also developed knowledge, techniques, instrumentation and personnel which made possible the subsequent rapid development of all phases of nuclear science, including nuclear medicine.

Diagnostic Applications

Current diagnostic procedures in which isotopes are used may be grouped into four categories: (1) dilution techniques, (2) localization or biochemical placement, (3) flow or diffusion measurement, and (4) metabolism studies.

The first clinical application of the dilution technique was made by Hevesy and Hofer in 1934 when they used deuterium in total body water studies. This principle was employed by P. F. Hahn and associates in early studies of red cell volume with radioiron. The dilution technique has been used in such studies as determination of blood and plasma volumes with Iodine 131-labeled serum albumin; red cell mass with Chromium 51, Iron 59, and Phosphorus 32;

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total exchangeable body sodium and potassium with Sodium 24 and Potassium 42; and total body water with deuterium and tritiated water.

An outstanding example of a clinical application of the localization or biochemical placement technique is the use of radioiodine for thyroid dysfunction studies. Hamilton and Soley demonstrated the basis for this diagnostic use of radioiodine in 1938. It is estimated that over half a million uptake studies have been done since that time.

This principle is also used in the differentiation and localization of benign and malignant tumors and cancer metastases. The type of tumors which have been successfully detected include ocular tumors with Phosphorus 32; liver tumors with Iodine 131-labeled human serum albumin, and with such positron emitters as Arsenic 74, Copper 64, and Zinc 65; and carcinomas of the thyroid with radioiodine.

Another versatile clinical procedure is the use of radioisotopes for flow or diffusion measurements. In 1937, Hamilton and Stone reported a study using the principle of this technique. They found radiosodium could be detected in the hand three to six minutes after oral administration. This principle also was employed by Quimby and Smith in 1943 when they used radiosodium to study circulation time in vascular diseases.

This procedure is now employed in studies of cardiac output, peripheral vascular disorders and blood volumes of extremities with Iodine 131-labeled serum albumin, and other circulatory investigations.

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The major contribution of isotopes to medical progress may well result from their use as analytical tools in investigating the body's complex chemical and physiological processes. Such use of isotopes began with Schoenheimer and Rittenberg's classic work which showed the dynamic turnover of metabolites.

Since their work, many materials have been labeled and traced through the complex body processes. These include photopholipids, sugars, proteins, nucleic acids, vitamins, hormones, amino acids and other metabolites.

Studies of the fate and role of metabolites have in some instances provided, or promise to provide, new diagnostic procedures.

Cobalt 60-labeled vitamin B-12 is currently used as an aid in diagnosing pernicious anemia. There is an absence of the Intrinsic Factor in patients with pernicious anemia which prevents the absorption of orally administered vitamin B-12. A lower percent of the vitamin appears in the urine of pernicious anemia patients than in normals. By labeling vitamin B-12 with Cobalt 60 it is possible to accurately determine, with the aid of a scintillation counter, the percent present in the urine. This procedure gives promise of becoming a routine diagnostic test.

Another such study is that of cholesterol metabolism. If cholesterol in the diet is labeled it can be traced unchanged into the blood. There a portion remains free in the plasma while others are incorporated into red blood cells or are chemically changed in the plasma. When tritium-labeled cholesterol was

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fed to normal persons and to patients with arteriosclerosis, the tritium activity in the blood fractions was found to be quite different to the two cases. The concentration of activity in the free cholesterol was normally higher than in other fractions making up the total. In arteriosclerosis it was lower. This type of test may lead to early diagnosis of the disease.

Therapeutic Applications

Radium has been used therapeutically many years in teletherapy devices, in surface applicators, and for insertion into tissue for local irradiation. With the discovery of artificially produced radioactivity, the possibility of a third mode of treatment was recognized. Radioactive forms of those elements which take part in body processes could be introduced into the body where it was expected that the body would then concentrate them in certain tissues for localized irradiation, but early hopes regarding this technique have not all been realized. Frequently, the radioisotope is not concentrated to a sufficient degree to allow its destruction of diseased tissue without damage to healthy tissues; therefore, biochemical placement of therapeutic amounts of lethal radiation can be relied upon only in certain types of cases. In these instances, valuable results are obtained.

The present therapeutic uses of radioisotopes may be grouped under the three modes of application mentioned above: (1) biochemical placement, (2) physical placement, and (3) teletherapy.

Biochemical placement is achieved principally in two ways: by the selective absorption of a material needed by a particular tissue for its function

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and by the differential turnover due to the increased use of a material in the more rapid metabolism of a particular tissue.

The best known and almost classic example of a special affinity between a tissue and a particular substance has been mentioned, that of the thyroid gland for iodine. The use of this selective action to introduce a sufficiently destructive amount of radioiodine to the gland is now considered a highly practical form of therapy for hyperthyroidism. Over 500 institutions in this country are using radioiodine for this purpose.

In 1955, Chapman and Maloff reviewed ten years experience with radioiodine in the treatment of hyperthyroidism at the Massachusetts General Hospital. During the ten year period, 520 hyperthyroids were treated. Seventy-five percent responded to a single dose of radioiodine, 12 percent required more than one dose to produce normal thyroid function, and 8 percent became myxedematous. The other 5 percent resulted in a variety of clinical reactions. Such satisfactory results have been experienced by many other groups.

Unfortunately, much less satisfactory results have been experienced with radioiodine in treating carcinoma of the thyroid. Some success, however, has been realized in treating metastases of the thyroid gland following removal of the gland.

An extension of the use of radioiodine in treating hyperthyroidism is the use of the same isotope to suppress normal thyroid function in patients

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suffering from angina pectoris and conjestive heart failure. The deliberately produced myxedema greatly decreases the load on the heart which results in a diminution of symptons. As could be expected, workers who had been using x-rays for irradiation of the thyroid for cardiac conditions, such as and his associates, were early users of Iodine 131 for this purpose.

Radiophosphorus has been used effectively in treating certain blood dyscrasias such as polycythemia vera and chronic leukemia. This therapy is based on a combination of a total body irradiation plus a somewhat more rapid turnover of radiophosphorus in the blood producing system. Radiophosphorus has certain advantages over total body x-irradiation. It is simpler to use and there appears to be less symptoms of radiation sickness.

Therapy by physical placement of radioactive materials began over 50 years ago with radium and radon. Artificial radioisotopes offer numerous ways of extending this mode of therapy.

Radioisotopes may be physically placed both in a solid form and as a liquid in an appropriate carrier or solution. As solids, they are placed on a body surface, inserted into cavities, or implanted into the tissues. As liquids, they are injected into cavities, mingled with body fluids for transport to inaccessible parts, or injected into tissues as a dispersed source in the extracellular spaces.

These methods of therapy by the physical placement of radioisotopes may be placed in three categories: (1) intracavitary, (2) interstitial, and (3) external.

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Both radioactive Cobalt 60 and radioactive Gold 198 have been used as intracavitary sources for therapy. Some groups are using Cobalt 60 solids for the intracavitary treatment of uterine cancer. Others have used radiocobalt for treatment of bladder cancer by introducing a nearly point source through a catheter into a bag which is distended to form a sphere in the bladder. Radiogold colloid when infused into the pleural or peritoneal cavities has proved effective in reducing effusions and ascites. The first report of the use of radiogold colloid in the treatment of effusions secondary to malignancy was made by J. H. Muller of Switzerland in 1949.

The use of reactor-produced radioisotopes as interstitial sources of radiation have primarily been limited to the use of Cobalt 60 and Gold 198, but Iridium 192 has been used by some groups. Up to the present, radiocobalt has been the most widely used. Primarily, this is because its use is so closely allied to that of radium with which radiologists have wide exeprience. The idea of using Cobalt 60 and other reactor produced gamma ray emitters for interstitial application occurred to a number of persons as soon as reactor-produced radioisotopes became available. W. G. Myers of Ohio State University was actually the first to employ Cobalt 60 as an interstitial source of radiation. Myers and colleagues also developed the technique of implantation which employs Cobalt 60 or Gold 198 seeds sheathed within nylon tubing.

Compared with radium, radiocobalt offers a number of advantages. These include easy handling with electromagnetic tongs, simple calibration, reasonable cost, and lack of radioactive decay products. Its clinical advantages depend on: beta radiation that can be easily filtered, making possible use of thin and

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inexpensive sheathing; use of multiple weak sources, permitting individualized tailoring of the dosage pattern; and flexible nylon sheathing, allowing easy insertion into irregular volumes of tumor tissue.

The primary advantage of radiogold as an interstitial source is that it has a short half-life and may be used in wire form encased in a non-radioactive metal sheath. It is possible, as with radon, to leave small sources in the irradiated tissue without subsequent removal. The less energetic gamma rays from Gold 198 than from Cobalt 60 permit easier shielding for protection and may provide an advantage in the ratio of tumor dose to total body dose.

Also included in interstitial therapy is the infiltration of radiogold 198 in colloidal form into inoperable nodes and neoplasms such as cancer of the prostate. This technique was originated by P. F. Hahn in Nashville, Tennessee.

The interstitial injection of radiogold for the treatment of prostate carcinoma was first reported by , , and of the University of Iowa in 1951. This mode of therapy has given promising results in those cases where the disease has extended beyond the confines of the prostatic gland, but in which there is no evidence of distant metastasis.

As external sources of radiation, isotopes are being applied in various ways to skin cancers and other malignant lesions on or near the surface of the body. By the use of pure beta-ray emitters, an intense effect is produced within the first few millimeters with no hazard to deeper normal tissue. Strontium 90

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is regularly mounted as such a source in devices which can be conveniently handled and applied to ophthalmic lesions. The use of a Strontium 90 applicator was pioneered in the United States by Friedell and co-workers at Western Reserve University. This group had felt the need of a beta-ray source to supplant the use of radon bulbs it had been using. By the choice of strontium they gained a half-life of 25 years instead of 3.8 days, simplicity of fabrication, and freedom from gamma radiation.

The Strontium 90 eye applicator has been used for the treatment of such conditions as vascularization, pterygium, vernal catarrh, tumors of eyelid and conjunctive, and infections such as tuberculous sclerokeratitis.

Solution of radioactive compounds, such as P 32-active sodium phosphate, may be absorbed in appropriately shaped pads and placed in contact with cancerous areas of the skin, as was done as early as nine years ago by the late Bertram V. A. Low-Beer. An appropriate beta emitter may also be incorporated in a plastic sheet for topical application.

Distance therapy by means of a gamma-ray beam from a concentrated radioisotope source is a direct outgrowth of teleradium and X-ray treatment. Certain radioisotopes, such as Cobalt 60 and Cesium 137, are extending this mode of therapy. A teletherapy device utilising such radioisotopes has several advantages over radium pack units. For instance, the treatment can be carried out at greater distances and the gamma rays are monoenergetic. In comparison with X-ray equipment giving comparable depth dose, teletherapy units using radioisotopes have greater maneuverability for moving field therapy making possible a wider variety of dosage patterns.

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The late L. G. Grimmett of M. D. Anderson Hospital, along with Marshall Brucer of the Medical Division of the Oak Ridge Institute of Nuclear Studies and others, pioneered the development of the Cobalt-60 teletherapy unit in this country. Grimmett designed the first unit to be constructed. Ironically, his death came only a month before the unit was completed. This unit was tested and calibrated at the Medical Division of the Oak Ridge Institute of Nuclear Studies and then transferred to the M. D. Anderson Hospital.

Much credit for the development of teletherapy units utilizing artificial radioactivity is due to the problems resolved by the Teletherapy Evaluation Board which was established by the Oak Ridge Institute and affiliated institutions.

The machines fall into two classes depending upon source strength. The source strength of "hectocurie" units are a few hundred curies while that of "kilocurie" units range up to a few thousand curies. "Hectocurie" units are less expensive and more easily moved than the "kilocurie" units. The latter permits a combination of faster and more distant treatment.

With the exception of radium units and one Cesium 137 unit, the 50 or more teletherapy machines in operation use Cobalt 60. Other hospitals have units in various stages of completion but slowness of production of Cobalt 60 has deterred installation. Cobalt 60 can be and soon may be produced in enormous quantities (megacurie amounts).

Cesium 137 offers some advantages over Cobalt 60 as a teletherapy source, chiefly because of its much longer half life (33 years vs. 5.3 years) and the reduced

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amount of heavy material needed to shield its less penetrating gamma rays. This isotope has not been available in large quantities, except for the 1540-curie source prepared at much effort for the first unit in Oak Ridge mentioned above. The shortage of cesium has been due to the slowness in development of procedures and facilities for separating it from uranium fission wastes. The Atomic Energy Commission's new cesium separation plant now under ~~production~~ construction should produce over 200,000 curies per year. Facilities can be developed to extract from fission wastes millions of curies per year of Cesium 137 and other fission products.

International Development

Most of the basic discoveries in radioactivity as well as in nuclear science originated in Europe. Yet, it has been noted that the medical use of artificially produced radioisotopes was impeded in the European countries due to their early entry into World War II. After the war's end clinical radioisotope programs were initiated in Canada, Great Britain, France, Sweden and several other countries. It is not possible to survey all the contributions of the European investigators to nuclear medicine, but the British contributions are particularly noteworthy.

Prior to 1948, when radioisotopes were made available from the nuclear reactor at Harwell, the British obtained their reactor-produced radioisotopes from the United States and Canada. Some of the early groups to begin clinical radioisotope programs in Great Britain were J. S. Mitchell at Cambridge; E. E. Pochin, at University College Hospital, London; W. V. Mayneord, the Royal Cancer Hospital in London; and the workers at the Medical Research Council Radiotherapeutic Unit

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at the Hammersmith Hospital. W. F. Mayneord and his co-workers developed Phosphorus 32 bakelite and plastic eye shells and buttons for the treatment of ophthalmic conditions, carried out therapy of the bladder using Sodium 24 and Bromine 82 in bags and were early users of Gold 198 colloid and grains interstitially. They were the first group to report the use of thulium for radiography of the human body, the first pictures being taken in November 1951; and one of the first to use scintillation counters in medical work.

Today over 50 countries are using radioisotopes clinically. Several countries have reactors and have established radioisotope distribution programs. By air shipment all isotopes, with the exception of those with very short half-life, are routinely available to all countries. However, with the world-wide interest in nuclear reactors stimulated by the United Nations Conference on Peaceful Uses of Atomic Energy at Geneva in August 1955, radioisotopes should soon be available from reactors close at hand in all portions of the world.

Neutron and Other Nuclear Radiations

A new form of nuclear radiation with possible medical application became available in 1932 with the discovery of the neutron. When sufficient quantities of deuterium became available to permit the use of deuterons as bombarding particles, the cyclotron became a producer of fairly high intensities of neutrons. This led in 1935, to the first tests of the biological effects of neutrons by J. H. Lawrence, P. C. Aebersold and E. O. Lawrence.

Soon Lawrence, Zirkle, Aebersold and others demonstrated using a variety of organisms that the biological effectiveness of neutrons as compared with X-rays

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(relative biological effectiveness) is different for various biological objects and tissues. Inasmuch as the radiation therapy of cancer depends to a considerable extent upon producing a greater biological effect on cancer cells than on normal cells, it appeared worthwhile to test this new radiation in the treatment of cancer. A collimation scheme was devised to produce a beam of fast neutrons with a sufficient depth dose for deep therapy. R. S. Stone, P. C. Aebersold and J. L. Larkin treated a considerable series of patients with fast neutrons with some encouraging results but this mode of therapy was finally abandoned because of late skin effects.

Demonstration of the very high capture cross-section for thermal neutrons by boron and lithium with the release of highly ionising nuclei led to tests in 1940, first by P. G. Kruger and later by Zahl, Copper and Dunning, of the possible utilisation of such thermal neutron processes in producing selective irradiation in biological material. Various procedures were tried for obtaining selective deposition of lithium and boron compounds in tissue, and irradiating with slow neutrons. Although some selectivity in radiation effect could be demonstrated using animals, it was not sufficiently great to warrant trials in human patients.

With the advent of the nuclear reactor the possibilities of neutron capture therapy have been reinvestigated. The group at the Berkeley Radiation Laboratory tried to obtain a selective irradiation with slow neutrons by deposition of enriched Uranium 235 in animal tissues. Sufficient localization of the Uranium 235 for clinical purposes was not attainable and also radioactive fission products were released into the general circulation.

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At Brookhaven National Laboratory W. H. Sweet, L. E. Farr and colleagues, using the high flux of thermal neutrons available in the nuclear reactor, have undertaken to develop procedures for neutron capture therapy in brain tumors. In this latest work several factors make for possibility of greater success than in previous attempts; highly enriched Boron 10 is used; highly collimated beams of thermal neutrons are available with thousands of times more intensity than with the cyclotron; treatment is attempted on the basis of short-term, non-equilibrium selectively lasting for matters of minutes; brain tumors, both because of localization and capillary characteristics, permit suitable neutron beam penetration and selective localization.

Although the number of patients treated at Brookhaven with neutron capture therapy has been limited, it has appeared worthwhile to continue the studies using a reactor designed specifically for medical purposes. It is expected that several medical reactors will be built in the United States in the next few years. These will be capable of not only providing intense beams of slow neutrons, but also producing radioisotopes and permitting gamma ray therapy from a secondary emitter or fission product gases.

High energy cyclotrons, such as the 184 inch machine at Berkeley, can now provide beams of protons with sufficient penetration for deep therapy in patients. C. A. Tobias in 1950, devised an irradiation scheme by which a well defined portion beam could be directed through very specific locations in experimental animals. It was found possible, for example, to destroy the pituitary gland with very little destruction of other tissue. Recently J. H. Lawrence, C. A. Tobias,

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and R. S. Stone have extended this principle to irradiation of pituitary gland of humans to study the effect of destruction of this gland on patients with extensive carcinoma. It is apparent that a proton beam with an energy of several hundred million volts, can effectively destroy a very localized region within a patient without damage to the skin or surrounding tissues. Although still very experimental, the use of very high-energy heavy-particle beams may have a definite role in the future of nuclear medicine.

Clinical Training

At present, progress in the medical use of radioisotopes is no longer seriously limited by the availability of material, instrumentation and suitable clinical techniques. The greatest single deterrent now is lack of adequately trained people.

Safe and effective use of radioactive materials requires that physicians devote necessary time and study to obtain adequate basic training and sufficient clinical experience. (Safe and effective use of radioactive materials requires that physicians devote necessary time and study to obtain adequate basic training and sufficient clinical experience.) Basic training should provide a working knowledge of the principles and practices of radiological health safety, radioactivity measurement, standardization techniques, instruments and biological effects of radiation. Clinical radioisotope experience should include active participation by the physician in the use of the radioisotope in patients and the evaluation of the suitability of the patients for radioisotope diagnosis or treatment. It also should include the measurement of doses, their administration, management of patients, and should be of sufficient duration to allow follow up.

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During early days of reactor isotope distribution the only way a physician could obtain training in clinical use of radioisotopes was to participate in the program of a pioneer group. The assistance of these pioneer workers gradually increased the number of groups qualified to use radioisotopes for clinical purposes. This resulted in a steady increase in the number of places where others could obtain the same kind of informal training.

Even today, almost ten years after the Commission's distribution program began, most would-be users of radioisotopes still have to rely largely on informal preceptor type training. This means that thousands of physicians still know little of isotope diagnosis and therapy. Most younger physicians being graduated from medical schools today likewise have learned little about isotope utilization.

Formal courses in clinical radioisotope techniques are offered in only about 30 hospitals and medical schools in this country. In most instances enrollment is very limited. Although coverage of material is thorough, unfortunately, many courses are inadequate in providing active participation in the measurement and clinical administration of isotopes. Courses are also often inadequate in length, establishment of specific prerequisites, selection of participants and final evaluation of competence.

For a healthy growth of nuclear medicine, every effort should be made by organizations within the medical profession to establish adequate training programs in the clinical use of radioisotopes. Certification of qualified persons by medical specialty boards should also be given encouragement.

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It has not been possible to mention all contributions to the development of nuclear medicine. Equally important to the ones mentioned are those made by the physicists, biologists, and chemists. They worked out the production and preparation of radioisotopes, determined decay schemes, measured the dosage of ionising radiation to tissues, obtained radioisotope toxicity data, provided methods and instrumentation for health protection, and developed new and refined medical instrumentation.

The scintillation counter, for example, is just one of the many notable contributions by nuclear scientists. It enables much greater sensitivity and selectivity in the use of radioisotopesfor medicine and research. Not only can smaller diagnostic doses be used than with a Geiger-Mueller counter, but electronic selection of pulses permits counting only radiation of a well defined energy range. Such energy selection allows measurement of primary radiation of a single energy without scattered and background radiation. This not only makes possible great improvements in diagnostic techniques, but opens up many new possibilities.

Recent development of an energy discriminating scintillation counter for medical use, a "medical spectrometer", has greatly reduced diagnostic dosages. P. R. Bell, one of its developers, reports thyroid uptake measurement with one microcurie of radioiodine and thyroid scanning with approximately five microcuries; this instrument is thus about 100-times more sensitive than the Geiger-Mueller counter.

Instrumentation has improved, yet, there is still much room for further refinement. Instruments could be developed for the physician which are even more dependable

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in operation, easier to maintain, less complex to use and lower in cost. Eventually devices for diagnosis with radioisotopes should be as simple and as dependable in use as other commonly used medical instrumentation.

Conclusion

Great advancement has been made in nuclear medicine in the last two decades. The work in the first decade with accelerator-produced radioisotopes laid a firm groundwork for development in the last decade with reactor-produced radioisotopes.

Today we have almost unlimited availability of most radioisotopes. Materials are processed to standard specifications and there is assurance that the supply will be dependable. Costs of reactor radioisotopes in general do not deter usage and as the number of users increases costs will become even less. Thousands of shipments are made each month to medical users from reactors in many countries. Reactors will be built throughout the world bringing an even greater and more ready availability of radiomaterials.

We have a tremendous body of knowledge related to nuclear medicine which has been accumulated by the physicist, chemist, biologist and clinician. Thousands of papers have already appeared in the scientific literature dealing with the use of radioisotopes in medical research, diagnosis and therapy. These papers reflect the growing utilization of radioisotopes in medicine. Even more important is the tremendous rate at which new knowledge in nuclear studies is being gained throughout the world.

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Remarkable developments in radioisotope methodology and instrumentation are extending the usefulness of radioactivity. Instruments now have much greater dependability, sensitivity and selectivity. These permit the use of smaller diagnostic doses, better quantitative studies, and more reliable monitoring devices. Such developments will continue to make possible better and safer handling techniques and superior clinical results.

The number of people trained in clinical radioisotope techniques since the inception of nuclear medicine has increased steadily. Although the number of qualified personnel has increased, more clinical training opportunities are a necessity to make more widely available the benefits of nuclear medicine. The medical profession should set high standards of clinical use and established criteria for medical radioisotope use similar to those of the other medical specialties.

On the basis of past developments and the present status of nuclear medicine we can expect a continuous and steady growth in techniques and uses. Several decades hence, nuclear medicine may begin to approach the use of X-rays in numbers of people benefited.

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