THE PRACTICE OF NUCLEAR MEDICINE

by

WILLIAM H. BLAHD, M.D.

Chief, Radioisotope Service, Veterans Administration Center, Los Angeles, California; Assistant Clinical Professor of Medicine, School of Medicine and Medical Physics Physician, Radiological Safety Division, University of California at Los Angeles

FRANZ K. BAUER, M.D.

Chief, Outpatient Services, Los Angeles County Hospital; Associate Clinical Professor of Medicine and Coordinator of Radioisotope Research, University of Southern California School of Medicine; Associate Clinical Professor of Medicine College of Medical Evangelists School of Medicine; Attending Specialist – Radioisotope Service, Veterans Administration Center, Los Angeles, California

BENEDICT CASSEN, Ph.D.

Chief, Medical Physics Section, Atomic Energy Project and Clinical Professor of Biophysics, University of California at Los Angeles School of Medicine; Consultant in Radioisotopes – Radioisotope Service, Veterans Administration Center, Los Angeles, California

Introduction by

PAUL AEBERSOLD, Ph.D.

Assistant Director for Isotopes and Radiation, Division of Civilian Application, United States Atomic Energy Commission

Foreword by

JOSEPH F. ROSS, M.D.

Associate Dean, Professor of Medicine and Radiology, School of Medicine, University of California at Los Angeles

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FOREWORD

JOSEPH F. ROSS, M. D.*

Nuclear Medicine – the use of nuclear radiations in medical diagnosis, therapy and research – has contributed greatly to the tremendous progress of medical knowledge and competence during the past quarter of a century. Radioisotope tracer studies have radically modified our entire concept of fundamental metabolic and physiologic processes and have established beyond question the fact that life and health are attributable to a precisely balanced state of dynamic equilibrium – and that death and disease are the result of a disruption and imbalance in this equilibrium state.

Radioisotope tracer methods have made possible, in normal and in diseased individuals, the determination of the actual *rates* at which vital functions are proceeding, the *chemical pathways* involved, the localization of the *sites* in the body where they occur, and the quantitative measurement of the *amounts* and *distribution* of substances in the body. Such studies have led to complete revision of our concepts of the pathogenesis of certain human diseases, have indicated promising new avenues of investigation, and have resulted in improved methods of therapy.

In addition to invaluable fundamental contributions, nuclear medicine has provided methods of great practical clinical value in the diagnosis and therapy of patients. Such measurements as cardiac output, renal excretory function, and blood volume have been greatly simplified by nuclear medical techniques, while such new tests as the quantitation of total body sodium or potassium, the measurement of the life span of an individual's own erythrocytes in his own circulation, and the measurement of the rate of thyroxine production of the thyroid gland are unique contributions of nuclear medicine. Radiocobalt radiation therapy appears to have definite practical advantages over roentgen therapy, and radioiodine therapy provides a unique and highly satisfactory method of control of hyperthyroidism.

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*Associate Dean, Professor of Medicine and Radiology, School of Medicine, University of California at Los Angeles.

Such techniques as these, and the many others detailed in this volume have become standard procedures in the major medical centers of the world. It is essential that practicing physicians be fully informed of the nature of nuclear energy, of its potentialities and its limitations in medical practice, and of its dangers if improperly utilized.

Doctors Blahd, Bauer and Cassen present in this volume a survey designed especially to inform the practicing physician of the great contributions that nuclear medicine can make to the health of mankind, and to present those studies and procedures which have particular applicability to the clinical management of patients. They detail the fundamental principles of nuclear physics lucidly "nonmathematically," and in a fashion designed to provide the physician with a clear understanding of the essential features of the nucleus and its emanations. The extensive personal clinical experience of the authors enables them to bring to the sections on clinical diagnosis and therapy a practical clinical viewpoint that will prove invaluable to the clinical reader. Since the authors have themselves employed the techniques which they describe, they are able to comment realistically on their virtues and shortcomings. These comments are made from the viewpoint of the practicing physician desiring to know the applicability of the techniques to his clinical problems, rather than from the highly technical viewpoint of the nuclear physicist or electronic engineer.

The illustrated section on instrumentation and laboratory design will be of great value to physicians who may wish to establish and equip their own nuclear medical laboratories.

The authors have performed much of their work while in association with the Radioisotope Service of the United States Veterans Administration, an organization that has fostered and greatly advanced the development of nuclear medicine and its application to the clinical management of patients. The wisdom and foresight of this governmental agency in making nuclear medicine available to veteran patients is in major respect responsible for the rapid application of fundamental nuclear medical discoveries to clinical medicine, and thus has contributed greatly and directly to medical progress.

INTRODUCTION

THE DEVELOPMENT OF NUCLEAR MEDICINE

By PAUL C. AEBERSOLD, Ph.D.*

HISTORICAL DEVELOPMENT

THE impact of nuclear energy, both for war and for 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 ionizing radiation. This encompasses a variety of radiations and a broad range of energies.

In retrospect, radiation, whether from atomic nuclei or from machines, has played a revolutionary role in the development of all fields of science, including medicine. However, the early use of radioactive materials in medical and biologic studies was limited. Prior to about 1934 the only radioactive isotopes available were the naturally occurring form which normally are present only in minute quantities in biologic systems. This limited the use of radioisotopes as tracer atoms in biologic investigations and precluded their use in diagnostic and therapeutic applications which involve metabolism of the radiomaterial in the patient.

A great impetus to the development of nuclear science was the

*Assistant Director for Isotopes and Radiation, Division of Civilian Application, United States Atomic Energy Commission.

discovery by Rutherford in 1919 that the structure of matter could be changed by bombarding elements with alpha particles from radium. He found that 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 were 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 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*, the result of an idea conceived by him in 1929. Instead of using a very high voltage for an initial acceleration of charged particles, the cyclotron employed a magnetic field and a series of accelerations to achieve high-energy particles with lower voltages. Lawrence and his associates at the University of California, Berkeley, built the first operating cyclotron late in 1930. Using the cyclotron, they were able to demonstrate nuclear transformation in 1932, almost immediately following that by Cockroft and Walton. This atom smasher, as it was then known, has proved to be the most useful and versatile of the man-made devices for effecting 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 hydrogen so that it could be used as a tracer in living systems.

Before the end of 1933, Lawrence and his colleagues developed a cyclotron capable of yielding a beam of deuterons 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 oroduce 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 not 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 greatly extended by the Joliots' discovery in 1934 of artificially induced radioactivity. They observed that, in bombarding aluminum foil with alpha particles, positrons continued to be emitted after the source of alpha particles was removed. Almost immediately the cyclotron became an invaluable tool for inducing radioactivity.

It then became possible 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 extended use of radiomaterials in medicine.

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

On December 2, 1942, Fermi and his co-workers at the University of Chicago achieved the first self-sustained nuclear chain reaction. From this monumental work has come the uranium nuclear reactor, which has virtually eliminated lack of availability as a major obstacle in radioisotope applications.

The *nuclear reactor* has proved to be an ideal production unit for radioisotopes having a neutron excess. Although not as wide a variety of radioisotopes can be produced in the reactor as in the cyclotron, what is much more important for extensive use, 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 millions of times greater than with the cyclotron and other accelerators. There are, however, a number of radioisotopes useful in biology and medicine which require cyclotron production: for example, beryllium-7, arsenic-74, sodium-22, magnesium-28, potassium-43, manganese-52, 54, iodine-125, and astatine-211.

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 Barnard Free Skin and Cancer Hospital in St. Louis, Missouri, on August 2, 1946.

Today, eleven years after the Atomic Energy Commission first began public distribution of radioisotopes, some 1,700 medical institutions in this country are using these materials. More than 50 countries have received radiomaterial from the United States since foreign distribution began in September, 1949. Since 1946, over 100,000 shipments have been made to radioisotope users from one Atomic Energy Commission facility, the Oak Ridge National Laboratory; a total of several hundred thousand shipments have been made from commercial suppliers and Commission facilities.

Radioactivity was associated with medicine thirty-five 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 a human being. Radium therapy was thus initiated and has now been developed over a fifty-six year period.

Over twenty 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 (lead-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 recorded tracer study with an enriched stable isotope but also the first application of the isotope dilution principle, which has found such widespread use in clinical studies.

In the fall of 1935 an artificially produced radioisotope was first applied to a biologic problem when Chiewitz and Hevesy used radioactive phosphorus as a tracer to investigate the distribution and excretion of that element in rats. About the same time Schoenheimer and Rittenberg used deuterium to show the dynamic turnover of metabolites.

Less than a year later on March 23, 1936, Hamilton and Stone in California employed the first artificially produced radioisotope for therapeutic trials. When they used cyclotron-produced sodium in three patients with leukemia and allied diseases, they also investigated the uptake and excretion of radiosodium in these patients.

On Christmas Eve of 1936, J. H. Lawrence initiated the therapeutic use of phosphorus-32 for the treatment of leukemia. The first successful therapy, however, did not begin until 1938, when J. H. Lawrence, L. A. Erf, L. W. Tuttle, and K. G. Scott treated a series of leukemic and polycythemic patients. A little later, in the early 1940's, several workers, such as C. A. Doan and B. K. Wiseman of Ohio State University and J. M. Kenney, L. F. Craver and L. D. Marinelli of Memorial Hospital, New York City, began using phosphorus-32 for the treatment of patients. Since that time radiophosphorus has proved to be the choice of many physicians for the treatment of patients with polycythemia vera or chronic leukemia.

The unique ability of the thyroid gland for selective uptake of iodine in relatively high concentration was known long before the era of radioisotopes. It is not surprising, then, that those studying the thyroid recognized early the potentialities of radioiodine as a research tool.

In 1938, soon after learning from Karl Compton that Fermi and his Italian co-workers had prepared radioactive isotopes of iodine, Hertz, Roberts, and Evans in Boston, Massachusetts, began to use

radioiodine for animal studies. They were able 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, and their findings substantiated those obtained by Hertz and his associates from their studies on laboratory animals. At 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 Hertz and Roberts, and Hamilton and Lawrence. Currently, as a result of over a decade of extensive study, many physicians believe radioiodine to be the best mode of therapy for hyperthyroidism, and it has received almost universal acceptance as an aid in the diagnosis of thyroid disease.

The capacity of metastatic carcinoma of the thyroid gland to accumulate radioiodine was reported by Keston, Ball, Frantz, and Palmer in 1942. In 1943, Seidlin, Marinelli, and Oshray began a long-term treatment of a patient with a metastatic adenocarcinoma of the thyroid using iodine-131. This experimental treatment was initiated after tracer studies showed that the radioiodine concentrated in the metastatic lesions. Later studies, reported by Marinelli, Foote, Hill, and Hocker in 1947, showed that only certain types of thyroid cancers accumulated radioiodine in significant amounts. Not all the early hopes for radioiodine for the treatment of carcinoma of the thyroid have materialized. It has been found that to obtain beneficial response from radioiodine the cancer cells must have or be induced to have an affinity for iodine similar to that of normal thyroid tissue.

Prior to the development of the nuclear reactor, the medical use of artificially produced radioisotopes grew slowly, primarily because few groups had sufficient quantities of radiomaterials, and the 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, a scientific team effort began which was 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

Currently, isotopes are used in the following diagnostic procedures: (1) physiologic localizations, (2) dilution techniques, (3) flow or diffusion measurements, and (4) studies of organic metabolites.

The most commonly used of these procedures involves the localization of a radioactive isotope in certain tissues or organs of the body. A labeled dose is administered and the selective uptake or specific absorption of the tracer agent by the organ is determined. The outstanding example of physiologic localization is the use of radioiodine (I^{131}) for the study of thyroid physiology. It is estimated that several million thyroid studies have been made with this material in the past twenty years. A few other isotopes are selectively concentrated in certain tissues to a much lesser degree, notably radiophosphorus (P^{32}), which is used in the localization of such malignant growths as ocular and brain tumors. The development of the scintillation counter, together with electronic selection of pulses representing a given energy range, has greatly extended the sensitivity and usefulness of localization techniques.

Dilution techniques are used in determining the size of various compartments or masses of the body, and the rate of exchange of materials between them. According to this method, the concentration of the dilution of a radioisotope in a body compartment is measured, and from this the volume of the compartment can be calculated. The isotope dilution technique has been of considerable clinical value in the determination of plasma volume, red-cell mass, and total body water.

Flow or diffusion tests are widely used in studies of the cardiovascular system. A small amount of an appropriate radioisotope is injected intravenously or interstitially, and the velocity of blood flow, the distribution in a certain part of the cardiovascular system, or the tissue clearance is determined. These procedures are now

used in studies of cardiac output, peripheral vascular disorders, and other circulatory investigation.

Radioisotopes show considerable promise as analytical tools in investigating the complex biochemical activity of the human body. Hundreds of isotope-labeled compounds have been used, including phospholipids, sugars, proteins, nucleic acids, vitamins, hormones, fatty acids, amino acids, and many other metabolites. Time alone will determine which of these many substances will prove to have real clinical value.

THERAPEUTIC APPLICATIONS

The present therapeutic uses of radioisotopes may be divided into three groups.

Biochemical placement is achieved principally in two ways: by the selective absorption of a material needed by a particular tissue for its function and by the differential turnover due to the increased use of a material in the more rapid metabolism of a particular tissue.

The 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 produce a sufficiently high radiation dose to the gland from radioiodine is now considered a highly practical form of therapy of hyperthyroidism. Over 500 institutions in this country are using radioiodine for this purpose.

Therapy by *physical placement* of radioactive materials began over fifty 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, injected into tissues as a dispersed source in the extracellular spaces, or placed in containers, such as plastic envelopes or tubing, to give easily controlled localized irradiation.

Distance therapy or *teletherapy* by means of a gamma-ray beam

from a concentrated radioisotope source is a direct outgrowth of teleradium and roentgen treatment. Teleradium devices have been used since 1918. The first devices were built in Great Britain just after the close of World War I, at which time the British Air Force allocated 2.5 grams of radium to the Medical Research Council. Reactor-produced radioisotopes now greatly extend this mode of therapy.

High-energy gamma-ray-emitting radioisotopes, such as cobalt-60 and cesium-137, can now be produced in very large quantities—hundreds of thousands of curies per year—at relatively low cost. Single compact sources are obtainable, equivalent in gamma-ray output to thousands of grams of radium. From example, cobalt-60, which is produced routinely with a specific activity of 50 curies per gram, permits kilocurie source dimensions of one to two centimeters. In comparison with roentgen-ray equipment giving comparable depth dose, teletherapy units are more compact and have greater maneuverability for moving field therapy, thus making possible a wide variety of dosage patterns.

CONCLUSIONS

Great advancement has been made in nuclear medicine in the past 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 most radioisotopes are in almost unlimited supply. Materials are processed to standard specifications and there is assurance that the supply will be dependable.

A tremendous body of knowledge related to nuclear medicine has been accumulated by the physicist, chemist, biologist, and clinician. Thousands of papers have already appeared in scientfic literature dealing with the use of radioisotopes in medical research, diagnosis, and therapy. These papers reflect the growing use of radioisotopes in medicine. In the field of medicine over a million patients per year are being diagnosed and treated with radioisotopes. Even more important is the tremendous rate at which new knowledge in nuclear studies is being gained throughout the world.

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. It is impossible to anticipate all the future benefits mankind will derive from this new field, nuclear medicine.

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WILLIAM H. BLAHD
FRANZ K. BAUER
BENEDICT CASSEN

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