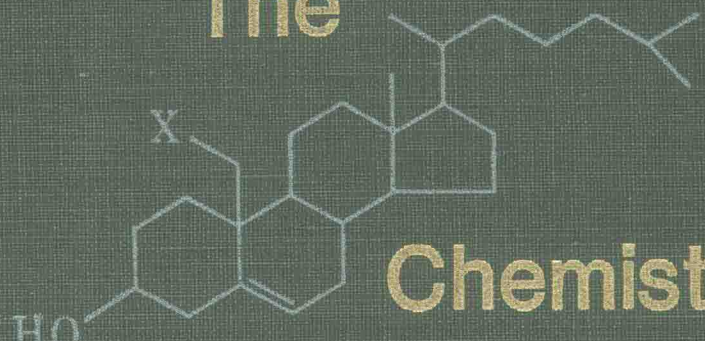
The Chemistry of Radiopharmaceuticals



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Edited by Ned D. Heindel, H. Donald Burns, Takashi Honda, and Luther W. Brady

FOREWORD

Cancer Management

IN 1977, THE AMERICAN CANCER SOCIETY estimates that about 690,000 people will be diagnosed as having cancer. These estimates of the incidence of cancer are based upon data from the National Cancer Institute's Third National Survey (1969–1971). About 230,000 or one-third of those in whom the diagnosis is established will be alive at least five years after treatment. About 115,000 of those who will die in 1977 might have been saved by earlier treatment.

The purpose of this series of monographs is to bring to the practicing physician, as rapidly as possible, the major strides being made in the diagnosis and treatment of cancer. A quiet revolution in cancer management is resulting from a combination of more appropriate and exact diagnostic techniques, the implementation of multidisciplinary, multimodal treatment techniques, the identification of factors influencing patient prognosis, and more appropriate and careful follow-up examinations and evaluations.

The series in *Cancer Management* will address the various problems inherent in diagnosis and treatment, with emphasis on new advances in those areas. Making such information available to the practicing physician in a coordinated, composite fashion will have a significant impact on earlier diagnosis, more appropriate treatment selection, and broader implementation of newer treatment information.

LUTHER W. BRADY
VINCENT T. DEVITA, JR.

PREFACE

GROWTH IN THE FIELD of radiopharmaceutical science has been virtually explosive. Aided by the development, over the last two decades, of ever more sophisticated imaging instrumentation—which makes possible precise localization of centers of isotopic concentration in the human patient—pharmacologists, physicists, biologists, and clinicians have tackled the task of discovering new radioactive pharmaceuticals for specific diagnostic purposes.

Agents are presently available for the delineation of lesions, malignancies, abscesses, and infarcts in the major organ systems. Through the instantaneous imaging capability of the gamma camera and the autofluoroscope, dynamic function and flow studies can reveal a wealth of diagnostic information about the heart, kidney, biliary tract, and vascular system.

Although a number of gamma- and positron-emitting nuclides play a useful role in contemporary nuclear medicine, the introduction of ^{99m}Tc into medicine around 1962 has been the major stimulus to the field. The chemical literature of 1956 contains little mention of technetium and its compounds. In 1966, approximately 15 papers appeared on synthesis, characterization, and utilization of its derivatives. By 1976, however, *Chemical Abstracts* was able to cite more than 130 chemical references per year. Reports and publications on the clinical utility of established technetium compounds far exceed those reporting new candidate radiopharmaceutical agents from the hands of the chemist.

The clinical acceptance of radiopharmaceuticals has been similarly impressive. It has been estimated that 12 million nuclear medicine procedures are performed annually and that more than 10% of all hospitalized patients are evaluated with a ^{99m}Tc derivative. The Society of Nuclear Medicine has grown to almost 10,000 members, and about 10% of these are engaged in purely basic science research and development.

While much has been accomplished in the last 20 years, much remains to be done. There still exist many problems in medical diagnosis to which radioisotopic procedures might contribute. Several agents already in clinical use do not represent the ultimate in safe dosimetry or in image quality and hence offer substantial opportunity to the chemist for modification and improvement. Dr. William Myers of Ohio State University Hospital, historian for the Society of Nuclear Medicine, reported at a recent national meeting: "We need more chemists to put the 'twinkling atoms' into compounds of physiological significance, for it is chemistry that will lead to new compounds of improved target/nontarget ratios."

It is the purpose of this book to provide an introduction to the field of radiopharmaceutical science and to illustrate how classic principles of drug design and of medicinal chemistry can be coupled with basic physiology, radiopharmacology, nuclear physics, and clinical testing to lead to new and useful radiodiagnostics.

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Outline of the Past and Future of Nuclear Medicine

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INTRODUCTION

While the growth of nuclear medicine has been continuous, certain events stand out as milestones: 1) the discovery of x rays by Roentgen in 1895; 2) the discovery of naturally occurring radioactivity in 1896; 3) the development of the tracer principle by Hevesy in 1913; 4) the first clinical studies with radioactive tracers in normal persons and patients with heart disease by Blumgart and his associates in 1927; 5) the discovery of artificial radioactivity by Joliot and Curie in 1934; 6) the building of the first medical cyclotron at the William H. Crocker Radiation Laboratory at Berkeley, California by Lawrence in 1939; 7) the construction of the first nuclear reactor in Chicago by Fermi in 1942; 8) the invention of the rectilinear scanner in 1951 by Cassen at UCLA; 9) the invention of the scintillation camera in 1957 by Anger at the University of California in Berkeley; and 10) the pioneering physiological studies of Hertz, Hamilton, Huff, and Sapirstein in applying radioactive tracers in physiological and subsequently in medical studies in the early 1940s.

Another crucial development occurred on August 2, 1946, when 1 mci of carbon-14 was delivered to the Barnard Free Skin and Cancer Hospital in St. Louis, Missouri. The first shipment was a milestone in the development of isotope technology upon which the field of nuclear medicine rests (1).

THE NATURE OF RADIOACTIVITY

One of the most important consequences of Roentgen's discovery of x rays was the demonstration that the passage of x rays through a gas increased the conductivity of the gas by the production of charged ions. This ionization theory of gases explained what happened when a discharge of

electricity passes through a vacuum tube. Further study of these cathode rays showed that they consisted of a stream of electrically negative particles, possessing an apparent mass much smaller than that of the hydrogen atom. Such experiments led to the elucidation of the atomic structure of matter by Rutherford in 1911 (2).

The impact that the discovery of x rays by Roentgen had at the time is illustrated by the fact that over 1000 articles and 50 books were published on roentgen rays in 1896 alone. Becquerel's contribution one year later was the demonstration that natural substances emitted radiations similar to x rays that were readily detected by their action on photographic plates and their ability to discharge electrified bodies.

Shortly after Becquerel had published his results on the radioactivity of potassium uranyl sulfate, Marie Curie decided that radioactivity would be a good subject for a doctoral thesis in physics at the Sorbonne. Using the electrometer that her husband Pierre had constructed, she measured the ionization produced by radioactive substances. Her first discovery in 1898 was that thorium was also radioactive. Her husband then joined in her work and together they announced the discovery of polonium in July and of radium in December of 1898. Marie Curie, her husband Pierre, and Becquerel shared the Nobel prize in physics in 1903, the same year in which Marie passed her examination for the Ph.D. degree.

It is interesting to ask what the world would be like if radioactivity had merely been thought a chemical curiosity and had been put on the back shelves of chemistry departments. The discovery of radioactivity led to the explanation of such diverse phenomena as x rays and the electronic structure of atoms, culminating in the verification of Rutherford's hypothesis of the atomic nucleus in 1911.

While the Curies were discovering and separating new radioactive substances, Ernest Rutherford and his associates were studying the nature of the rays and the products that resulted when radioactive decay took place. In 1899 Rutherford studied the radiation from uranium and showed that there were two kinds of rays. One had little penetrating power but enormous power to ionize air; he called these "alpha rays." The other had more penetrating power but less ionizing power; he called these "beta rays." The next year Villard demonstrated that radium gave off a third kind of ray, more penetrating than either alpha or beta rays and that could not be deflected by a magnetic field; these were called "gamma rays" (3).

In 1902 Rutherford, working with Soddy, published two papers in which they showed that one element could be transmuted into another during the process of radioactive decay. By 1911 he had developed the concept of the nuclear atom. As Rutherford, Soddy, Hevesy, and their co-workers studied the process of radioactive disintegration and the transmutations of matter that occurred during radioactive decay, they began to realize that some of the products could not be separated. For example, when radium D was

separated from pitchblende, it could not be separated from lead. As Soddy studied these substances, he came to the conclusion that they could not be separated because they were the same chemical element (4). In 1913 he suggested in a letter in *Nature* that these substances be called *isotopes*, because they occupy the same place in the periodic table, chemically identical and differing only in atomic mass (5).

THE TRACER PRINCIPLE

As in the case of x rays, the tracer principle was based on the use of ionizing radiation to yield information. Here the source of the radiation is within the body of the patient from which it is emitted rather than being transmitted through the body from an external source of x rays. The idea of using radioactive indicators occurred to Hevesy in 1912 when he was working in Manchester, England, with Rutherford. Rutherford had received several hundred kilograms of pitchblende from Austria. This material contained radium D together with large quantities of lead. In his Nobel lecture delivered in 1944, Hevesy recalled, "When I met Rutherford one day in 1911, he said 'my boy if you are worth your salt you will try to separate radium D from all that lead.' " Hevesy then goes on to tell how he labored in vain for almost 2 years, but failed completely. And then he continues: "In order to make the best of this depressing situation I decided to use radium D as an indicator of lead." Thus the tracer concept was born. In 1924 Hevesy described his idea of using radioactive isotopes as tracers for elements in biological as well as chemical systems (6). These were first used in studies of the circulation of lead and bismuth in plants and animals (7). The most important consequence of the invention of the tracer principle was the elucidation of the dynamic state of body constituents. This principle is an extension of the principle of the constancy of the internal environment first proposed by Claude Bernard, who pointed out that the concentration of chemical constituents in body fluid are usually kept within a very narrow range and disturbances of these concentrations result in disease. This concept of the constancy of the internal environment or homeostatis has been one of the foundations of modern medicine. Hevesy and then Schoenheimer extended this concept by introducing the concept of the dynamic state of body constituents.

The story of the development of techniques and methods for the practical use of radioisotopes is the story of the accomplishments of Georg Hevesy. In 1913 with Paneth, he used the lead isotope radium D as a tracer for lead in the determination of the solubilities of lead sulfide and lead chromate in water (8). Ten years later he used thorium D (another isotope of lead) to trace the movement of lead in beans (6). In 1924, working with a dermatologist who was interested in bismuth salts for the treatment of syphilis, he studied the distribution of bismuth (radium E) in rabbits (7). In 1931

he used Radium D to determine the lead content of a number of rocks, thereby introducing the concept of the isotope dilution technique (9). In 1934, after the discovery of deuterium by Urey, Hevesy obtained some heavy water from Urey and used it to measure the mean lifetime of water in the human body and the speed of exchange of water between the body of the goldfish and its environment (10,11). In 1935 Hevesy and his co-workers used phosphorus-32 to study the metabolism of phosphorus in rats and man. In his initial experiments he made ^{32}P by bombarding sulfur with neutrons produced by a radium–beryllium source, but later he used a higher specific activity material made by Lawrence with his newly invented cyclotron (12–14).

In 1936 Hevesy began to receive phosphorus-32 from Ernest Lawrence, who invented the cyclotron in Berkeley, California (15). Short-lived isotopes such as potassium-42 and sodium-44 began to be produced for the first time. In 1935 Chiewitz and Hevesy submitted a letter to the editor of *Nature* in which they said "our results strongly support the view that the formation of bones is a dynamic process. The bone continuously taking up phosphorus atoms which are partly or wholly lost again and are replaced by other phosphorus atoms" (12). These classic experiments were extended by Schoenheimer, who pointed out that the apparent stability and constancy of the body is the result of delicate balances among innumerable chemical reactions occurring simultaneously. Even before Hevesy's experiments with phosphorus-32, sodium-24, and potassium-42, Blumgart and his co-workers in Boston carried out the first clinical studies with radioactive isotopes. Over 50 years ago they published their first results of injecting solutions of radon salts intravenously, monitoring the time of arrival of the tracer in the opposite arm as a measure of the velocity of the circulation in normal persons and in patients with a variety of heart diseases (16). These experiments were 14 years before radioiodine was first used to study the metabolic activity of the thyroid gland.

In his Nobel lecture Hevesy stated, "The application of isotopic indicators open new lines of approach not only to the solution of known problems but also by directing our attention to trains of thought not previously considered. Isotopic indicators open the only way to determine the rate, place, and sequence of formation of many molecular constituents of the living organism. The very existence of such methods was instrumental in opening new trains of thought in demonstrating the dynamicity of metabolic processes in concentrating our interest on the problem of velocity of fundamental biological processes."

In 1936 Hevesy and Levi exposed samples of rare-earth compounds to a radium–beryllium neutron source to detect impurities in them, thus inventing the method of neutron activation analysis (17).

In 1919 Rutherford showed that when an alpha particle strikes a nitrogen atom, a proton and an oxygen atom are given off (18). This was the first case

of the artificial transmutation of one element into another. Two of the most significant discoveries made in the study of nuclear transmutations were the discovery of the neutron by Chadwick in 1932 (19) and of artificial radioactivity by Irene Curie and Pierre Joliot in 1934 (20). Chadwick discovered the neutron by bombarding beryllium with alpha particles from polonium; the Joliot-Curies showed that when aluminum was bombarded with alpha particles, the aluminum remained radioactive after the alpha source was removed.

Enrico Fermi combined these two discoveries to show that neutrons were ideal particles with which to bombard stable atoms to produce artificial radioactivity. Using neutrons, Fermi and his colleagues made many artificial radioisotopes. The cyclotron, developed by Lawrence beginning about 1930, proved to be a much more effective means of producing artificially radioactive substances than the radium–beryllium source. Subsequently, the discovery by Hahn and Strassman in 1939 that barium was formed when uranium was bombarded by neutrons and the explanation by Meitner and Frisch of the fission of uranium led to the first construction of a nuclear reactor by Fermi in 1942. This permitted very-large-scale production of radioactive isotopes, and nuclear medicine was ready to be born.

BIOLOGICAL APPLICATIONS

To understand the impact of the tracer principle in biology and medicine we need to look at the status of biomedical research prior to the development of tracer methods. Prior to the development of radioactive tracer methods, the only method for studying the biochemistry of the body was to measure the way in which various elements and compounds were assimilated, distributed throughout the tissues, converted into other compounds, and finally eliminated from the body. In order to observe the manner in which a living organism metabolized an element, it was necessary to administer enough of it so that a detectable increase of the amount in the body was produced. Such procedures frequently disturbed the normal chemistry and physiology of the organism and the data obtained do not present a true picture. Secondly, with the stable tracers it was not possible to distinguish the administered substance from the naturally occurring substance. The use of radioactive tracers eliminated many of these problems.

The initial experiments of pioneers, such as Hertz, Hamilton, and coworkers (21, 22), were concerned with the study of elements, for example, phosphorus and iodine. They carried out extensive investigations of the unique capability of the thyroid gland to accumulate radioiodine in relatively large quantities. The thyroid gland can concentrate the iodine it receives from the blood by a factor of 10,000. Although other organs were found to be capable of the selective uptake of certain elements, none ap-

proached the capacity of the thyroid. It was not surprising that radioiodine was accepted eagerly as a new research tool by thyroid physiologists (23).

Hertz and his associates first demonstrated in 1940 the rapidity with which iodine is accumulated in the thyroid of rabbits. These observations were confirmed in patients with hyperthyroidism by Hamilton and Soley, who measured the accumulation of radioiodine by placing a Geiger counter against the neck. Normal persons and patients with hyperthyroidism, nontoxic goiter, and hypothyroidism were studied with the aid of this technique (24). In collaboration with colleagues, including I. Chaikoff, they conducted a detailed series of experiments in animals that elucidated knowledge of the intermediary metabolism of iodine (25). They also began to use radioiodine to suppress the function of normal thyroid tissue in rabbits and dogs.

It is interesting to read verbatim the description of these investigators: "The results of the experiments with labelled iodine bring out three points of interest in consideration of the possible use of radioiodine in the treatment of hyperthyroidism. They show that the thyroids of patients with thyrotoxicosis accumulate and retain a large proportion of the administered radioiodine; that the thyroid tissue can be destroyed selectively without apparent damage to the other tissues of the body; that accumulated iodine is deposited selectively in the regions of the thyroid tissue which are most hyperplastic. . . . The selective irradiation of these areas should produce a relatively greater depression of the hyperplastic portion of the gland than of the normally functioning regions. It is deemed inadvisable to employ radioiodine as a therapeutic agent in hyperthyroidism until experimental studies of the action of large doses have been conducted" (26). Fortunately these fears were unwarranted, and radioiodine therapy has now been safely used in hundreds of thousands of patients throughout the world. Hamilton also added that: "The available experimental information on the failure of cancerous thyroid tissue to accumulate significant quantities of radioiodine does not indicate that this agent will be of any value in the therapy of carcinoma of the thyroid." Unfortunately this prophetic statement is about 90% correct.

THE FUTURE

In his book *Introduction to the Study of Experimental Medicine,* Claude Bernard conceptualized the relationship between physics, chemistry, and the investigation of living organisms (27). He wrote that physiologists make use of "instruments and procedures borrowed from physics and chemistry in order to study and measure the diverse vital phenomena whose laws they seek to discover." In all physiological investigations, "the grand principle is not to stop until one has reached the physico-chemical explanation for the phenomena one is studying."

In the mid-nineteenth century, there was much argument about the re-