Georg Charles de Hevesy: The Father of Nuclear Medicine

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J Nucl Med Technol 1996; 24:291–294

It is especially timely and fitting at the end of the first quarter of a century of the existence of the Society of Nuclear Medicine to realize that the commemorative presentation at our annual meeting will be designated henceforth as the Hevesy Nuclear Medicine Pioneer Lecture. In this manner we will be reminded each year of "the one who started it all" and thereby acknowledge our gratitude and indebtedness to him for the immense impact of his intuition on our lore. Much of the basic origins of nuclear medicine stemmed from the insights and the seminal contributions of Professor Hevesy. The consuming drive of his scientific curiosity and his indefatigable enterprise made of him the towering intellectual genius that he was.

Manifestations of Hevesy's manifold and vividly imaginative pioneering investigations, which spanned more than a half century, were chronicled fittingly in the 1047 pages of two monumental volumes published in 1962 (*1*) and aptly titled, *Adventures in Radioisotope Research*. Here are reprinted, in translation into English from as many as four other languages, a selection of 100 of his nearly 400 publications, together with intercalations of numerous commentaries of invaluable historical content.

Although Hevesy's training lay principally in the field of physical chemistry, his interests were highly diverse and his prodigious endeavors penetrated into many areas of science. Specifically important to us in nuclear medicine was his discovery of the indicator tracer method of analysis and the initiation of applications of it in biomedicine.

It was Hevesy who, in 1923, first used a naturally radioactive isotope, 10.6-hr ^{212}Pb (ThB), to study the uptakes of labeled lead ions from dilute solutions by the roots, stem, leaves and fruit of vicia faba (horse bean). He used an electroscope to assay the relative amounts of radioactivity present in ashed samples of parts of the plants. Because of the extreme sensitivity of physical radioassay methods, he carried out these experiments with such minuscule concentrations of lead as to avoid the toxic properties of it. He proved also that the lead taken up by the plants was present in them in ionizable form (*1,2*).

The following year Hevesy published with Christiansen and Lomholt (*1*) the results of the first experiments in animals in which radiochemical methods were employed. They used 5.0-day ^{210}Bi (RaE) to label and to follow the circulation of bismuth in the bodies of rabbits after intramuscular injections of antisyphilitic medicaments containing bismuth. Similarly, they used 22.3-yr ^{210}Pb (RaD) as a radioindicator to follow the excretion and the distribution of lead in several organs after injection of labeled lead hydroxide mixed with olive oil (*1*). The measurements were made at the Institute of Theoretical Physics (now The Bohr Institute) at the University of Copenhagen, where Hevesy pursued many of his investigations. There he enjoyed the appreciative interest of his cherished friend, Niels Bohr.

While Hevesy was in Manchester a dozen years previously, Professor Ernest Rutherford importuned the young chemist to separate radioactive ^{210}Pb from its admixture with the large amounts of nonradioactive lead in the laboratory there by saying to him (*1*) "If you are worth your salt, you separate radium D from all that nuisance of lead." For two years, Hevesy tried in vain to carry out the separation by chemical methods. Failing in this, he concluded the great sensitivity of physical methods for measuring radioactivity would make imponderable amounts of ^{210}Pb an excellent radioindicator tracer to "represent" nonradioactive lead atoms in qualitative and quantitative processes. Thus, Hevesy's fertile imagination converted adversity into advantage and the concept of radioindicator chemistry was born! Frustration from his failure serendipitously had led to triumph and to the discovery of the most sensitive method of analysis.

When Hevesy went to the Vienna Radium Institute early in 1913, he found Dr. Fritz Paneth had been working quite independently there on the same problem, and with the same fruitless results. The two young chemists then decided to publish jointly their findings on the chemical inseparability of ^{210}Pb (RaD) from nonradioactive lead. They also published together the use of ^{210}Pb as a radioindicator tracer to analyze quantitatively the slight solubilities of lead sulfide and lead

Reprinted from: Myers WG. Georg Charles de Hevesy: the father of nuclear medicine. *J Nucl Med* 1979;20:590–594.

chromate (*1,3,4*). In these papers they introduced the method and the technical terminology, "radioelements as indicators." These two publications in 1913 constituted the first in which radioindicator tracers played a unique role in chemical analysis. Twenty-five years later in their book (*5*), *A Manual of Radioactivity*, these two pioneers clearly defined their term, "indicator."... In problems of this kind, in which the radioelement is not the object but the agent of the investigation, we say that the radio-elements serve as "indicators,' (*5*).... An *indicated element* is an element containing a small amount of an isotopic element which serves as an indicator for the purpose of detection or measurement." (*5*).

While with Rutherford in Manchester in 1911, Hevesy performed a delightfully imaginative and practical experiment to demonstrate that the landlady in his boarding house was recycling food. It seems she had been serving freshly-prepared meat only on Sunday and then disguised it in servings of hash, goulash and other forms the rest of the week. When Hevesy cautiously suggested it would be tasty to have freshly-cooked meat served more frequently than once a week, she retorted indignantly that she served it every day. Hevesy was a sparse eater; and so, to prove her assertion was not true, he "spiked" a scrap of leftover meat on his plate one day with a tiny amount of a radioactive material. A few days later he brought an electroscope to the table to demonstrate to her that the hash served that day was radioactive. "This is magic," she exclaimed! This labeling of food, under such piquant circumstances, may have been the first tagging experiment in the life sciences, although, unfortunately, it was of course not published formally.

Hevesy used radioindicator methods during the decade between 1913 and 1923 in several radiochemical determinations; and many of his publications were coauthored with Paneth. Some of his papers involved colloid chemistry or electrochemistry, and others were concerned with self-diffusion in metals (*1*). Also, partial separations of isotopes of mercury and of chlorine were effected with Bronsted.

In 1923, Hevesy and Coster found the missing element 72 and named it hafnium, after the Latin name for Copenhagen, in honor of the city where the discovery was made, and of which Hevesy was particularly fond.

Hevesy and Hofer, in 1934, first used in medicine an enriched stable isotope to determine the rate of elimination of water from the human body (*1*). They drank dilute deuterated water, HOD, discovered by Urey only two years previously, and assayed the further isotopic dilution of the deuterium in their urine. From their results they concluded the average time a water molecule spent in their bodies was 13 ± 1.5 days.

"Chance only favors the prepared mind," wrote Pasteur. Hevesy's brilliant mind and previous pioneering experiences with applications in biomedicine of natural radionuclides, and with a stable one, had prepared him fully and well to embrace immediately new opportunities to exploit the discoveries of radioindicators of "biochemical/physiological" elements similarly. Frederic Joliot and Irene Curie discovered artificial radioactivity early in 1934 by creating in their laboratory in Paris positron emitters of two "biological" elements, 2.5-min ^{30}P and 10-min ^{13}N (*6*). Within several months, Fermi and his students used a radon-beryllium neutron source in Rome in their discoveries of a large number of radionuclides of many elements. Among them was 14.3-day ^{32}P.

Hevesy recognized immediately the potential applicability of this convenient radioactive form of a "vital" element to extend his radioindicator method to studies of diverse natural metabolic processes. Within a year after ^{32}P was discovered he published with Chievitz (chief of surgery at the Finsen Hospital in Copenhagen) the first radioindicator study in the life sciences with a man-made radionuclide (*1*). "Radioactive Indicators in the Study of Phosphorus Metabolism in Rats" appeared in *Nature* in 1935 (*7*). This landmark contribution was reprinted in *The Journal of Nuclear Medicine* in 1975 (*8*), along with my commentary and with a picture I made of Hevesy in 1950. Phosphorus-32 "can be utilized as an indicator of inactive phosphorus in the same way that the radioactive isotopes of lead, bismuth and so on were formerly used as indicators of these elements."

A strong neutron source was immersed in 10 liters of carbon disulfide for some weeks to generate about a microcurie of ^{32}P in the $^{32}S(n, p)^{32}P$ transmutation (*1*). The ^{32}P thus obtained was converted into ^{32}P-phosphate before placing it on bits of bread to feed to rats. Geiger-Müller detectors were used to assay the amounts of ^{32}P found in various organs and excreta as a function of time. Among interesting findings was that the average time spent by a phosphorus atom in the rat was about two months. This first biomedical study with artificial radioactivity led to the conclusion there is a rapid turnover of phosphorus atoms in bone. *Thus emerged the concept of the dynamic state of the body constituents.*

Hevesy now hit his stride in applying radioindicators in biomedicine. As radionuclides of additional "biochemical" elements (^{24}Na, ^{42}K, etc.) soon were discovered and became available, chiefly by generating them with cyclotrons, he devoted his time increasingly to applying them in studies of a large variety of metabolic and physiological processes. The results found in most of these were reprinted in 1962 (*1*), as noted previously.

His interests remained broad, however. In 1936, only four years after Chadwick discovered the neutron in England, Hevesy and Hilde Levi used it in Copenhagen in their discovery of neutron radioactivation analysis. This sprang from studies of the rare earth elements (*1*) and of several other elements (*1*).

Radioactive Indicators was the title of Hevesy's 556-page book, published in 1948 (*9*). It is a landmark contribution in which he succinctly summarized in quite complete review the basic concepts and the experimental findings in our subject to that time. Hevesy did not function in isolation but kept abreast of developments in applications of indicator tracer methodology in biomedical laboratories throughout the world. This book constituted also a turning point in the history of nuclear medicine; for, almost all of the myriads of measurements made by the numerous investigators had depended on assays made in vitro, chiefly of beta particles, by means of Geiger-Müller detectors or electroscopes.

Hevesy himself seems to have used methods of assay in vivo by means of penetrating gamma rays little, if at all. In 1948, also, a new era dawned with the discovery of the NaI(Tl) scintillation detector by Hofstadter (*10*). Its much greater efficiency of interaction with gamma rays and other advantages soon led to the "inside-out" assays and imaging that now dominate the explosive expansion of Hevesy's concepts into clinical nuclear medicine.

Hevesy received the Nobel Prize for chemistry in 1943 "for his work on the use of isotopes as tracer elements in researches on chemical processes." In his Nobel lecture on "Some Applications of Isotopic Indicators" (*1,11*), he stated, "The most remarkable result obtained in the study of the application of isotopic indicators is perhaps the discovery of the dynamic state of the body constituents. The molecules building up the plant or animal organism are incessantly renewed."

Near the end of his Faraday Lecture in 1950 (*1,12*) on "The Applications of Radioactive Indicators in Biochemistry," Hevesy said:

> The application of isotopic indicators opened 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 concentrating our interest on the problem of the velocity of the fundamental biological processes. . . . The indicator chemist is to some extent an historian, highly interested in the past of atoms, molecules and molecular aggregates. He has a great concern in the distinction of how far molecules present in the tissue are "old" or "new." . . . He wishes to know when the potassium atoms present in the tissue cells left the circulation.

Another instance of Hevesy's keen sense of history was illustrated in his handwritten letter to Ernest Lawrence on January 14, 1938 when he thanked Lawrence for mailing sufficient ^{32}P to carry out investigations about milk formation, "It is always a sign of appreciation to keep letters, but it is a sign of utmost appreciation to treat letters as we did treat yours. A trace of phosphorus penetrated the envelope . . . and this induced us to dissolve your letter and to recover the trace of phosphorus it contained. When historians will once describe your life history I hope they won't omit this incident, showing how precious your letters were." In those days radioisotopes simply were airmailed in ordinary envelopes! Hevesy was highly appreciative of Lawrence's generosity, for the cyclotron in Berkeley was the only major source of the radionuclides he needed to pursue the numerous ideas overflowing from his mind.

I first met Hevesy at the Symposium on Radiobiology held at Oberlin College in 1950. There he presented an extensive paper on "Ionizing Radiation and Cellular Metabolism" (*13*). Hevesy always was ahead of his time! He was among the first to apply radioactive indicators in studies of the effects of ionizing radiations (*1*). Also, he and his colleagues first used indicator tracer methods to study cancerous tumors.

My doctor of medicine thesis on "Applications of The Cyclotron and Its Products in Biomedicine" was written early in 1941, only seven years after artificial radioactivity was described (*6*). I appreciated the role this epoch-making discovery already had had on Hevesy's insights and increased productivity by noting that 16 of the 87 references cited in the review were authored by Hevesy and coworkers (*14*).

Hevesy's firsthand acquaintanceships with Niels Bohr, Marie and Irene Curie, Frederic Joliot, Albert Einstein, Fritz Paneth, Ernest Rutherford and many other of the "greats" in basic nuclear science made of him an eyewitness historian of many momentous events. That he was an able reporter of these was reflected in his giving of our second Nuclear Pioneer Lecture on June 15, 1961 in Pittsburgh at the eighth annual meeting of the Society of Nuclear Medicine, "Marie Curie and Her Contemporaries: The Becquerel-Curie Memorial Lecture" (*15*). Hevesy already had been made an honorary member of the Society of Nuclear Medicine, in 1959.

The Gesellschaft für Nuklearmedizin began to honor Hevesy a decade ago by awarding the Hevesy Prize and by the giving of the Hevesy Lecture annually. This prize first was given to Dr. H. Saul Winchell at the meeting in Zurich in 1969, and he gave the lecture the first time then also. At the Gesellschaft meeting in 1976 in Berlin, Dr. Henry Wagner gave the Hevesy Lecture; and his appreciation of the scientist led him later to coin the aphorism (*16*), "Biochemical motion—What Hevesy conceived, we now perceive." How true! Dr. Rosalyn Yalow gave the Hevesy Lecture and received the Hevesy Medal in Madrid in 1978 at the 16th annual meeting of the Gesellschaft für Nuklearmedizin. In her essay on "Radioimmunoassay: Past, Present and Potential," she expressed regret for not having met Hevesy, but regarded him through his book in 1948 (*9*) almost as having been her teacher. In her lecture when she received the Nobel Prize for medicine in 1977, she acknowledged Hevesy as a scientific progenitor of her career (*17*).

Hilde Levi worked closely with Hevesy as an assistant and knew him so well as to become his principal biographer. She published in 1976 a delightful portrayal of him and his methods in the laboratory, as well as of some of his warm and kindly interpersonal relationships (*18*), "George Hevesy and His Concept of Radioactive Indicators—In Retrospect." "He was possessed by his scientific ideas which dominated his thinking so much he did not have time for other activities." Her historical essay was the first paper to be published in the new *European Journal of Nuclear Medicine* (*18*).

A decade earlier, Levi published a shorter sketch about Hevesy (*19*). His "inexhaustible stream of new ideas, his dynamic personality, his incredible memory for everything done or read, and his apparently effortless endurance—he never could sleep more than a few hours each night—brought about his ever-presence at all odd hours of the day in different laboratories scattered all over the city of Copenhagen."

Her obituary concerning Hevesy in 1967 (*20*) sketched his lifework in summary outline. It includes a photograph of him and a reliable source of reference to serve as a complete and correct bibliography of his 397 publications.

"Hevesy wrote practically everything by hand" (*18*). The treasured longhand letters I received from him reflect the warmth, humility, modesty and considerateness of the man. His extensive correspondence resulted in his stating a point laconically. "Radioiodine-123 is a most useful substance" appeared in his letter to me in July 1962.

One finds much in McCagg's documentary book in 1972 (*21*) about the origins of five scientists in modern Hungary whom he considered to be geniuses, and Hevesy was one of them.

Hevesy was born August 1, 1885 in Budapest, Hungary and completed his secondary school education at the Piarist Grammar School. His academic studies began at the University of Budapest, continued in Berlin, and he received his PhD degree in chemistry and physics from the University of Freiburg in 1908. After appointments in many laboratories in several countries, he became professor of physical chemistry at Freiburg, 1926–1935. He left there to go to the Bohr Institute in Copenhagen, where he stayed during the occupation until 1943 when he settled down in the Institute for Organic Chemistry of the University of Stockholm. He died in a clinic in Freiburg on July 5, 1966.

Numerous honors were bestowed on Hevesy in addition to the Nobel Prize in 1943 and the Atoms for Peace Award in 1959. He regarded especially highly his election to be a foreign member of the Royal Society of London and his being awarded the Copley Medal by it in 1949. He received more than a dozen honorary degrees; and he may have been unique insofar as four of them were honorary doctor of medicine degrees. Four faculties of medicine thus indicated the esteem in which they held Hevesy for his basic contributions to medicine.

Nuclear medicine is endowed with an especially rich and variegated heritage. Paraphrasing Newton, "We stand on the shoulders of giants;" and our activities stem from an integration of some of the insights of no less than three dozen Nobel laureates and the sagacity of many other gifted scientists. Distinctly notable among our forebears was Georg Charles de Hevesy. At the end of the first 25 yr of the Society of Nuclear Medicine, we opportunely and appropriately demonstrate our maturity when we acknowledge our cognizance and appreciation of the magnificent scientific legacy we derive from Hevesy and recognize him to have been our inspirational leader and our principal intellectual forefather.

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