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The Nobel Laureate George de Hevesy (1885-1966) - Universal Genius and Father of Nuclear Medicine

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Abstract

The scientific work of the universal genius the Nobel Laureate George de Hevesy who has discovered and developed news in physics, chemistry, geology, biology and medicine is described. Special attention is given to his work in life science which he had done in the second half of his scientific career and was the base of the development of nuclear medicine.

Keywords: George de Hevesy; Radionuclides; Nuclear Medicine

Introduction

George de Hevesy has founded Radioanalytical Chemistry and Nuclear Medicine, discovered the element hafnium and first separated stable isotopes. He was an inventor in many disciplines and his interest was not only focused on the development and refinement of methods, but also on the structure of matter and its changes: atoms, molecules, cells, organs, plants, animals, men and cosmic objects. He was working under complicated political situation in Europe in the 20th century. During his stay in Germany, Austria, Hungary, Switzerland, Denmark, and Sweden he wrote a lot papers in German. In 1962 he edited a large part of his articles in a collection where German papers are translated in English [1]. In the reference, the original German and the English translation are given. About his life and work we can found some biographical books and articles [2-5]. Hevesy wrote an autobiographic article in the collection of his scientific papers [6].

Family and education

Hevesy was born in August 1, 1885 in Budapest as the fifth child of a wealthy aristocratic Hungarian Jewish family and was educated by private teachers and until 1903 in the catholic school of the piarists in Budapest where sciences had a high level. He converted to the catholic religion when he started his advanced studies in Budapest. He continued studying in Berlin and Freiburg, and at the end of 1908 he finished there with a Ph.D. He knew the growing importance of electrochemical processes in metallurgy, worked later in a metallurgical enterprise in Hungary and in his thesis Hevesy determined the solubility of sodium in molten sodium hydroxide which he found responsible for the bad yield in the electrolysis of sodium. After his time as assistant in the Institutes of Physical Chemistry in Zurich and Karlsruhe he went to Ernest Rutherford in the Physical Institute in Manchester where his interest changed drastically. Hevesy studied the properties of the radioactive elements by means of physicochemical methods and demonstrated the possibility to use radioactive elements as indicators [7-9]. In 1912 Niels Bohr came to Manchester and his lifelong friendship with Hevesy begun.

Scientific discoveries and developments

The invention of the indicator method

The most important invention of Hevesy is the indicator method. When he came to Manchester some of the discovered radioactive elements are chemically similar and inseparable. Later they were identified as isotopes. At that time nobody understood that the same element isolated from different minerals could be in one case radioactive and in another not. In 1900 the radiochemist Andreas Hofmann had isolated radio-lead from uranium minerals which Rutherford found identically with his decay product of radium and named radium D (RaD) and which later was identified as the isotope of lead ^{210}Pb. It was assumed that radio-lead and lead from uranium free minerals are different chemical elements. In 1913 Rutherford wrote in his book about radioactivity that *"it would be desirable to extract pure radium D from pitchblende. After one month its beta activity would be 30 times more than the activity of same weight of radium"*. In the cellar of the institute some hundred of kilograms of lead chloride obtained after extraction of uranium and radium from Jachymov pitchblende containing large activities of the valuable RaD were stored [10]. Rutherford said to Hevesy: "*My boy if you are worth your salt you will separate the RaD from all that nuisance of lead*".

Though Hevesy was not able to separate these two substances he had the idea to take advantage of this impossibility when he used the inseparable radioelement as tracer. He wanted to demonstrate his idea in the determination of the very low solubility of lead chromate in water using RaD as an indicator for lead. Knowing that Friedrich Paneth in the Radium Institute in Vienna had no success in separation of RaD and lead, too, he suggested him in the last days of 1912 to work together and label lead nitrate with RaD, converting it to chromate and determine its solubility by measuring the fraction of activity of RaD in the filtrate. With this work they demonstrated the use of radioactive isotopes as tracer. It was done in the Radium Institute, because of its better possibilities for chemical experiments [11,12]. In the same year Hevesy got his lecturing qualification at the University of Budapest and travelling between Manchester, Vienna and Budapest.

He applied the indicator method in Physical Chemistry using RaD, E (^{210}Bi) and F (^{210}Po) as indicators. During tea time in Rutherford`s institute in 1913 he said to Moseley that it would be interesting to trace the way of the components of tea through the human body. Since that time he was looking for the possibility to apply the indicator method to investigate physiological processes. But the known radioactive isotopes of the elements were not essential in biology. In Manchester he became friendship with Henry Moseley and was much impressed of Moseley´s invention of the law of correlation of X-ray energy with the atomic number of the used target element and he saw the possibility to look with this method for undiscovered elements and to determine elemental concentrations. He couldn´t co-operate with Moseley because before he was travelling the channel World War begun and forces Moseley to go to the army and one year later Hevesy, too. After the war Hungary became independent from Austria and in 1918 he substitute for a chair for physics and when in 1919 the communist Bela Kun was leader of the Council Republic he obtain an own chair for physical chemistry at the Budapest University.

Separation of isotopes, discovering of hafnium in Copenhagen, and developing X-ray fluorescence in Freiburg Breisgau

After some month Romanian troops invaded Hungary, Admiral Horthy came to power, and Hevesy lost his chair and the allowance of teaching; therefore in 1920 he emigrated to Denmark [13]. In Copenhagen his friend Niels Bohr found a place for him in the laboratory of Johannes Nikolaus Brönsted (1879-1947) in the Institute of Physical Chemistry and provided for him funds from a foundation. Together with Brönsted he separated isotopes of mercury, chlorine and potassium. When the laboratories in the new Institute of Theoretical Physics in Copenhagen headed by Niels Bohr were installed, Hevesy continued experiments with radioactive isotopes. He studied the transfer of lead from the soil in different parts of a bean plants using ^{210}Pb [14]. In Copenhagen Bohr was interested in the X-ray spectra of different elements and invited Dirk Coster to install a spectrometer in his institute. Hevesy has planned the search of the unknown element number 72. In 1922 together with Coster Hevesy analysed zircon minerals by X-ray spectroscopy and they found the lines of the until unknown element number 72 which they named hafnium [15,16]. They improved the accuracy of the X - ray spectroscopy for further investigations and Hevesy separated and purified hafnium by fractionated crystallisation of potassium zirconium fluoride.

After the discovery of hafnium Hevesy received offers from German universities and took a chair at the University in Freiburg. From 1926 to 1934 he was professor and director of the institute of Physical Chemistry and beside his Hungarian citizenship he became citizen of the state Baden in Germany. In Freiburg he applied the X-ray spectroscopy for the determination of trace elements in minerals and rocks and developed together with his assistant und students the X-ray fluorescence analysis and applied it for the determination of trace elements in rocks [17]. Searching for radioactive isotopes of rare earth elements he discovered the radioactivity of samarium.

When his friend Harold Urey (1893 - 1981) had discovered the heavy hydrogen, he sent a few litres water containing 0.6% of D_2O to Hevesy, who used it immediately for the investigation of hydrogen exchange in a fish and in his own body [18]. This was the first use of a stable isotope as indicator. He very loved Freiburg, where he had a good position and possibilities for research and teaching. Under the colleagues he found many friends, interesting discussions with them and with colleagues from abroad which he proposed to give lectures in Freiburg. His stay in Freiburg enabled a heyday of sciences at the university, and when his mother has been died in 1931 he saw in Freiburg his homeland. In 1934 after establishment of the Nazi regime in Germany he immigrated again to Copenhagen for working in the institute of his friend Niels Bohr. After his arrival the physiologist August Krogh (1874-1949, Nobel Prize 1920) called on him because he was interested in biological investigations with heavy water.

After the discovery of artificial radioactivity by Frederick and Irene Curie radioactive isotopes of essential elements became available for physiologic research

Through the years Hevesy was sad that biochemical processes could not be investigated with the help of the known radioisotopes because the biological relevant elements were stable. In 1928 he wrote to his friend Paneth that in some years a revolution in nuclear physics would take place. When the artificial radioactivity was discovered by Joliot and Irene Curie he was able to use

^{32}P and other radioactive isotopes as indicators in life sciences. But before he produced ^{32}P he studied radioisotopes formed by the neutron activation of the rare earth elements (r. e. e.) which he had obtained from Auer v. Welsbach. With Hilde Levi who must emigrate from Germany, too, he produced a source of neutrons containing a mixture of 600 mg radium, 400mc of radon and beryllium powder. After neutron irradiation of the r. e. e. they observed an extremely high activation yield of dysprosium and europium. Then he took advantage of this, determined both elements in other r. e. e. and on this way he founded the neutron activation analysis [19,20].

Experiments with ^{32}P

Hevesy´s main interest was focussed on the new possibility of using radioactive indicators which he started with ^{32}P. He used a Rn-Be neutron source for the irradiation of carbon disulfide to produce ^{32}P. With this isotope he studied the distribution and the kinetic of exchange of phosphorus in different parts of animals, beginning with teeth and bones [21,22]. For this work he first co-operate with the surgeon of the Finsen Hospital Ole Chievitz, a friend of Niels Bohr. Labelled phosphate administered to rats and the specific activity in the phosphorous in blood and in the skeleton was compared, getting the surprising result of the continuous exchange of phosphorus in the bones. When they published the results the biologists would not believe them. Then he was working with many scientists in different laboratories in the field of nuclear physiology. Hevesy continued his study on the uptake of ions by plants, which he started first with ^{210}Pb in 1924 with Linderström-Lang and Nielsen of ^{32}P, and later with Irma Anderson-Kottö of ^{65}Zn by neurospora [23,24].

With Hilde Levi and O. Rebbe Hevesy injected labelled phosphatides produced in a chick embryo in a fertilised egg and studied the rate of renewal of ATP. With Adrian Aten jr. he observed that phosphate penetrated in comparison to labile organic molecules very slowly into erythrocytes [25]. This enabled them to use labelled erythrocytes to the determination of blood volume [26]. Then he studied the renewal of adenosine triphosphate (ATP) together with Jakub Parnas from Lwow (Poland) [27].

The activity of ^{32}P obtained by his neutron source was low and therefore he couldn´t do so many experiments. For the determination of the activity were extremely long counting intervals necessary.

His work in Copenhagen was sponsored by the Rockefeller – Foundation. They financed Hevesy, three assistant and an accelerator for the production of radioisotope and nuclear physics. A Danish company enabled the installation of a cyclotron, too. Because both accelerators came into operation very late he asked his friend Ernest Lawrence (1901-1958, Nobel Prize 1939) who had developed and constructed a cyclotron in Berkeley to send him ^{32}P. It was very helpful for his research that Martin Kamen from the cyclotron laboratory who was responsible for producing radioactive isotopes for chemical and biological research applied him with ^{32}P. Kamen wrote September 13, 1939: [28]

Dear Dr. Hevesy:

Unfortunately this letter does not contain the usual phosphorus sample, but we propose to send you some radio-phosphorus within the next fortnight. In order to guarantee delivery of some of this material, we are going to send three or four separate letters instead of in one big sample, inasmuch as present conditions in Europe entail some risk of any given sample's being lost. I hope your researches will not be seriously hampered by this delay.

Yours sincerely,

M. Kamen

In 1940 he investigated with Ladislaus Hahn the formation rate of desoxyribose nucleic acid (DNA). While ^{32}P shows the renewal of ATP in the growing liver in DNA take place an incorporation of ^{32}P in a large extend [29].

Later Kamen sent ^{24}Na and ^{42}K for investigations of the penetration through cell walls. Hevesy was much impressed that within the first minute a very large fraction of the sodium ions in spite of potassium ions in the circulation was replaced by extra vascular sodium [30]. For the investigation of the penetration of ions through the capillary wall they used ^{24}Na, ^{32}P, ^{36}Cl, ^{42}K, and ^{85}Br which they had produced by the cyclotron of the Institute of Theoretical Physics in Copenhagen and heavy water [31]. The transfer of water through cell walls he had investigated with C.F. Jacobsen from the Carlsberg Laboratory [32].

Biochemical investigations in Sweden

In 1943 when it became dangerous to stay in Denmark he fled to Stockholm where he continued his work with radioactive tracers in biology, physiology and medicine in the Institute of Organic Chemistry. He had co-operated with its head Hans von Euler-Chelpin (1873-1964, Nobel Prize 1929) even during his stay in Copenhagen. In the first month he could live with his wife and the two youngest daughters Ingrid and Pia in an apartment room above the laboratory, whereas his eldest daughter Jenny and his son Georg lived in suburbs. In 1944 he was awarded by the Nobel Prize for Chemistry for the year 1943 for founding the indicator method and its application in biology and medicine. The Nobel Prize enabled him to become a Swedish citizen. In Stockholm Hevesy was working on different problems in laboratories of different institutes and cooperated with a large number of scientists.

Hevesy was working with Euler and his assistant about the metabolism of nucleic acids in cells of a sarcoma tumour [33]. In the Institute Hevesy studied with G. Dreyfus the effect of X-rays on the incorporation and with J. Ottensen the formation of DNA in organs of rat after injection of labelled phosphate [34]. The largest daily formation was found in the mucosa of the small intestine, and the lowest in the brain [35]. Than Hevesy investigated together with Euler the effect of irradiation with X-rays on the incorporation of ^{32}P into DNA, on the metabolism bicarbonate, glucose, and fatty acid, the formation of nucleonic acid, and the turnover of nucleic acid in retrograde sarcoma [36]. The DNA of the Jensen Sarcoma of rats exposed to X-rays showed a depression of the rate of formation of DNA [37]. Beside this main topic he studied with G. Häggqvist the toxic effects of heavy water on animals [38].

Hevesy extended with Arne Forssberg the radiation studies to the incorporation of ^{14}C into DNA in the organ of growing mice which was depressed in contrast to the incorporation of proteins [39]. His investigation he continued later with the biochemist Einar Hammersten from the Karolinska Institute [40].

In 1955 Hevesy focussed his interest to haematology and was co-operating with colleagues of the institute of the haematologist Hugo Theorell (1903-1982, Nobel Prize 1955). With Roger Bonnichsen he studied the metabolism of iron with ^{59}Fe, with G. v. Ehrenstein the iron transfer to the embryo, and with Forsberg the effect of radiation on tissues [41-43]. The investigation was continued with the haematologist Dieter Lockner [44]. In the department of Kottmeier in the radium clinic in Stockholm Hevesy determined the half-time of the transportation of iron from the cells into the plasma before and after irradiation of patients suffering carcinoma uteri [45].

The last years of his life, honours, illness, and death

Hevesy was working in laboratories in Stockholm until 1961. His application of radioactive indicators in biochemistry and medicine opened the door for developments, which we can see in the large number of Nobel Prize Winners of Medicine who used this tool for their inventions. Rosalyn Yalow and Salomon Berson demonstrated in 1960 the later named radioimmunoassay, where a radioactive labelled antibody reacts with a hormone or another biological substance and allows its determination in extremely low concentration. They had injected radioactive insulin into an insulin-taking diabetic patient. Yalow obtained the Nobel Prize in 1977 [46]. The long-time fruitful experiences with radioactive labelled antibodies for the determination of hormones and tumour markers were important for new developments with antibodies which emit UV light by chemical reactions.

The organ imaging with radiopharmaceuticals has been continuously developed from the detection of ^{131}I in the thyroid gland by scintillation counters to the application of the Anger camera until the now used single photon emission computed tomography (SPECT) and positron emission tomography (PET). Nowadays the physicians have a number of tools based on Hevesy`s developments which enables mankind a better and longer life.

Hevesy was awarded by a lot of prices, honorary degrees and memberships. The Copley medal of the Royal Society was for him the most prestigious. In the United State he was awarded by the "Atoms for Peace Award". The Society of Nuclear Medicine (SNM) which was founded in March 1953 initiated in 1960 the George Charles de Hevesy Nuclear Pioneer Award and the Hevesy Nuclear Medicine Pioneer Lecture. In 1958 Hevesy became honorary member of the SNM. He was named "father of nuclear medicine". After World War II he often visited institutes in the United States and was impressed of the development of nuclear medicine and its equipment's [47]. On this visits he met in La Jolla (CA) the family of his eldest daughter Jenny who had married Gustaf Arrhenius the grandson of the well-known physic-chemist Svante Arrhenius.

In Copenhagen and Stockholm he did not obtained any appointment and lived from the endowment of the Nobel Prize, funds from projects and a pension from Germany which he obtained as indemnification. In 1949 after the World War II he renewed his contact with his friends in Freiburg and in the following years he spent some weeks in Freiburg, visited the meetings of the Nobel Prize winners in Lindau and arranged lectures of his famous friends in the Institute of Physical Chemistry. For his time in Freiburg the radiobiologist Hanns Langendorff reserved for him a room in his institute. For starting of nuclear medicine in the medical clinic he contacted Lawrence in Berkeley who provided radioisotopes. Hevesy was member of the international Society of Nuclear Medicine and was honour president of the European Society of Nuclear Medicine founded 1963 in Freiburg.

Hevesy was acquainted with a lot of famous scientists of different disciplines all over the world. He solved problems in different disciplines with relatively simple experiments. On his way through physical, inorganic, analytical, radio- and biochemistry, geology, physics, physiology and nuclear medicine he invented important methods. Most time he was working as a guest in a laboratory in different countries. There he had to adapt himself at the interest of the head of the laboratory and the experimental possibilities. When he must flee from a country he had to change his colleagues, his equipments, and the topic of his work. It is extremely surprising that he could receive important results under such circumstances even at an advanced age.

In his last years he suffered from lung cancer. Ludwig Heilmeyer had offered him to come to his clinic at the Freiburg University. There he died at July 6, 1966, and was buried in Freiburg - Littenweiler. His daughter Ingrid lived in Freiburg and felt responsible for the family grave. When she became ill and no more was able to take care for it, the family found help by the Hungarian Academy of Sciences. In April 19, 2001, the Academy arranged a reburial at a cemetery in the centre of the town of his birth where his children and grandchildren participated.

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