PROFESSOR DE HEVESY TRACES RADIOISOTOPE HISTORY

Professor George de Hevesy, who was a pioneer in the field of radio-active tracers, prepared the following paper for the IAEA symposium on Radiochemical Methods of Analysis, held at Salzburg in October 1964. Professor de Hevesy was born in Budapest in 1885. He studied in Budapest, Berlin and Freiburg, and spent some years at Zürich when Einstein was there. In 1911 he went to Manchester to work with Rutherford and there "witnessed some of the greatest discoveries in the history of physics". At the end of 1912 he visited the Vienna Institute for Radium Research, where he worked with Paneth, and in 1913 applied the method of labelled lead for the first time. After the first world war, he worked at the Institute for Theoretical Physics in Copenhagen; since 1943, his chief activities have been in Sweden.

In 1923, with Coster, he discovered the element hafnium. He made notable discoveries on the mobility of ions, and isotope separation, and his work on radioisotope tracers, which has had important biological applications, won him the Nobel Prize for Chemistry in 1943.

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Rutherford's favourite child was the alpha-particle. At an early date he considered it very probable that alpha-rays are composed of helium atoms carrying two positive charges. He determined numerous properties of these rays and together with Geiger worked out a method of counting their number. This was the first step which later led to the construction of the beta-ray counter worked out by Geiger and Müller in Kiel. Rutherford then concentrated his interest on the study of the scattering of alpha-particles, studies which led to the discovery of the nucleus of the atom. He always attacked the most pertinent problems, choosing the best way of attack and interpreted his results in a most straightforward way. During the years I worked under him I did not observe a single case in which he deviated from the above path. In the early teens of this century, the study of the properties of the nucleus of the atom was his main interest, but several other problems were also investigated by him simultaneously, among others the properties of beta-rays. In view of the very soft beta-rays emitted by radium-D, a strongly active preparation of this radioactive body was needed. Rutherford had quite a quantity of this radioactive body in his institute, but as it was embedded in large amounts of lead chloride, this material was quite useless. The radiolead chloride was a gift of the Austrian government and was obtained when extracting radium from Joachimstal pitchblende.

One day I met Rutherford in the cellar of the institute where some hundred kilograms of radiolead chloride were stored. He remarked that, if I were worth my salt, I would separate the radium-D from all that nuisance of lead. Being a young man I was an optimist and I was pretty sure that I should succeed. Though I made the greatest efforts I failed. Pondering about my failure I arrived at the conclusion that, if radium-D could not be separated from lead, it should be possible to add pure radium-D of known activity to some lead compound to carry out chemical reactions with this "labelled"

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lead and to follow the path of lead ions with the aid of radioactive measurements. Pure radium-D was available by treating glass tubes in which radium emanation decayed with dilute acid. Such tubes were much used in those days in cancer therapy.

The institution most concerned with radium emanation, later called radon, in 1912 was the Vienna Institute for Radium Research. This induced me to visit the Vienna Institute in November 1912, where I met Fritz Paneth who was an assistant there and I learned that he had also made abortive efforts to separate radium-D from radiolead. Spending Christmas in Budapest I wrote to Paneth on one of the last days of 1912 to suggest the labelling of lead nitrate with radium-D, converting it to sulphide and determining the solubility of this compound by measuring the fraction of radium-D present in the filtrate. Paneth had a counter proposal: he wished to study the electrochemistry of polonium and to test the correctness of the formula of his schoolmate Karl Herzfeld, but he added to his second letter the remark that he had no objection to carrying out the investigation proposed by me.

Early in January we started our investigations, studying by using labelled lead sulphide and also lead chromate, the solubility of these compounds. In those days the Geiger counter was not yet available and we made use of a gold-leaf electroscope in our experiments. In the next investigation, the deposition voltage of radium-D and of radium-E was studied before and after the addition of a varying amount of lead and bismuth. While carrying out the above-mentioned and other early investigations, we had not only to try to find answers to our problems but also to collect arguments to counter the views of those who were not willing to recognize the close resemblance of radium-D and lead. We could influence the deposition voltage of radium-D by adding lead, but lead only, and to influence the rate of dissolution of a layer of thorium-B by adding lead, but not by adding bismuth or thallium, demonstrating that radium-D, thorium-B and lead are chemically practically identical elements. The name, isotope, was only coined by Soddy in December 1913.

By studying the interchange between solid lead sulphate and the labelled lead ions of a saturated lead sulphate solution, Paneth demonstrated that only the uppermost layer of the solid lead sulphate participates in an interchange process. A very different behaviour is shown, as found by me, by a metallic lead surface. Hundreds of atomic layers of the surface of a lead foil interchange with the labelled lead ions of the surrounding solution and vice versa. This is presumably due to local electrode processes which try to eliminate differences in the electropositivity of different parts of the metallic foil.

FIRST FREE RADICALS DISCOVERED

In the winter of 1917 when I was stationed in the Carpathians, Stefan Meyer, the Director of the Radium Institute, wrote me that Paneth had made a great discovery – he had proved the existence of a volatile polonium hydride. This was not a great discovery in view of the fact that sulphur, selenium and tellerium, the lower homologues of polonium, form volatile hydrides. But it led to great advances in the hands of Paneth. He added dilute hydrochloric

acid to a magnesium-polonium alloy, led a nitrogen stream over the mixture and passed the gas stream into an emanation electroscope. From the discharge of the latter, Paneth deduced the presence of a volatile polonium hydride in the electroscope. Being a conscientious man, he repeated the experiment with thorium-C-labelled bismuth. It was generally assumed that bismuth had no volatile hydride and he expected that in such an experiment, the electroscope would not be discharged. Contrary to his expectations, a discharge took place. These experiments led to the discovery of a volatile bismuth hydride and later of a volatile lead hydride. The last mentioned discovery had far-reaching consequences. When investigating bismuth hydride, Paneth had inserted a glass tube between the thorium-C sample and the emanation electroscope, and when he heated the glass tube, the thorium-C hydride decomposed and accordingly no activity reached the electroscope. He carried out similar experiments with the volatile lead hydride which he discovered and then studied the behaviour of other volatile lead compounds such as lead tetramethyl. When heating a part of the quartz tube through which a hydrogen stream carrying lead tetramethyl passed, he obtained in the heated part of the tube, a lead mirror, the methyl being split off. When carrying the methyl-containing hydrogen through another tube containing another lead mirror, the latter disappeared. He deduced from this and similar observations the existence of a free methyl radical of very short life. In a hydrogen stream of 2-mm pressure, half the methyl disappeared within 0.006 seconds. The existence of free radicals was discussed by Kolbe (among others) 80 years before Paneth's experiments. What Kolbe thought was the methyl radical was in fact ethane. It was the ingenious experimental arrangement of Paneth which alone enabled free methyl, the first free radical, to be discovered. Since then free radicals have played an important role in organic chemistry, radiobiology and other branches of science. Paneth contributed to chemistry through numerous investigations of great importance, but his most important contribution was the discovery of free radicals.

INDICATOR ANALYSIS

Radioactive indicators played an important role in showing whether the precipitation of a compound is quantitative or not. Phosphorus, for example, is often determined as ammonium phosphomolybdate. It was formerly assumed that by this method, all the phosphorus present in a solution was precipitated. When, however, the precipitation was carried out with labelled phosphorus, 1.5 per cent of the activity, and thus of the phosphorus, was found to be present in the filtrate. By changing the conditions of precipitation, e.g. by the reduction of the nitric acid content of the solution to 1 per cent, a more complete precipitation of the phosphorus content of the solution could be obtained.

Even before artificial radioactive isotopes were available, natural radioactive isotopes were used in indicator analysis. In the quantitative determination of chromate, for example, the chromate solution is added to one containing a known amount of thorium-B-labelled lead. The precipitate obtained is removed and the activity of the filtrate determined. From the ratio of the

activities of the latter and of the lead solution added, the amount of precipitated lead and correspondingly that of lead chromate can be calculated.

ISOTOPE DILUTION

The first application of radioactivity in analytical chemistry is as old as the discovery of the radioactivity. The intensity of uranium radiation was found by Becquerel to be proportionate to the amount of uranium present.

If we add to a mixture of elements a radioactive isotope of one of the components of the mixture and recover a fraction of this element, its specific activity will be a measure of the amount of the element in question present in the mixture. The method of isotope dilution is based on these considerations. We add, for example, 10 milligrams lead, as nitrate, and radium-D or thorium-B of negligible weight having an activity of, say, 100,000 counts per minute to a solution of a mineral. If we recover 1 milligram of lead with an activity of 10 000 counts, we can conclude that the mineral did not contain lead. If, however, we recover 1 milligram of lead with only 1 000 counts, we must conclude that the mineral contained 9 milligrams of inactive lead.

The first application of isotope dilution analysis was the determination of minute amounts of lead in 1929, carried out by Hobbie and myself. We added to the solution of rock samples, radium-D of negligible weight and of known activity and deposited both the lead present in the samples and the radium-D added as the peroxide on platinum anodes. If 100 per cent of the radium-D added was deposited, 100 per cent of the lead content of the sample must have been deposited as well, and the weight of the deposit properly indicated the lead content of the sample. If, for example, only 80 per cent of the radium-D was recovered, we had to divide the weight of the deposit by 0.8 to arrive at a correct value for the lead content of the rock samples investigated.

THE WATER CONTENT OF THE BODY

Shortly after terminating our first investigations with Paneth, I was back in Manchester in April 1913 and happened to indulge in a cup of tea with the late J.G. Mosley, the founder of X-ray spectroscopy. We spoke about the application of radioactive indicators carried out with Paneth and I happened to remark that it would interest me to follow the path of the cup of tea taken in through my body, Mosley was an ingenious man and a man of great vision, but he considered my wish to be more than utopian. Two decades had not yet elapsed when Urey discovered heavy water and by doing so made it possible to fulfil my wish. Urey very kindly presented me with a few litres of labelled water which contained only 0.6 per cent of heavy water, but this was enough to determine the dilution which, for example, one litre of this water suffered in the course of a few hours in the human body (a time interval which suffices for a homogeneous distribution of the heavy water in the total body water). The excretion of labelled water in the course of a few hours is negligible. About 60 per cent of the body weight was found to be composed of water. We have here a very clear-cut example of the application of the method of isotope

dilution. If we administer 1 millilitre of deuterium and find in the body fluids, for example, in the blood plasma, after the lapse of a few hours, a deuterium concentration of 1/50 000 we can conclude that the body contains 50 litres of diluting water.

After the discovery of tritiated water this hyperheavy water was often used as an indicator in the determination of the body water. The most extended application of the method of isotope dilution to the determination of the body water and other plasma constituents was carried out by Moore *et al.*

The principle of isotope dilution proved to be of great value in determining the magnitude of different body components, as for example the red corpuscle volume or the plasma volume. In the determination of red corpuscle volume, blood is incubated at body temperature for half an hour, for example, in the presence of labelled sodium orthophosphate. The phosphate penetrates fairly slowly into the red corpuscle but, once entered, the ion interchanges rapidly with some of the acid-soluble organic phosphorus. The concentration of the organic acid-soluble phosphorus in the red corpuscle is considerably greater than that of orthophosphate. As a result of this and the process mentioned above, the red corpuscle acts as a somewhat imperfect mousetrap for phosphorus-32 which leaves the erythrocyte much more slowly than it enters. Ten minutes suffice to get a homogeneous distribution between the injected labelled and the circulating non-labelled red corpuscles and the loss of phosphorus-32 in the course of this time is negligible, though it turns out to be about six per cent in the course of one hour.

A fully stable labelling of red corpuscles can be achieved by introducing iron-59 in their haemoglobin. This can only be done *in vivo*, we therefore need a donor and correspondingly the iron-59 labelling is not suitable for clinical use. Similarly, the first devised method in which the labelled plasma was transfused to another rabbit and the dilution of the activity of labelled phosphatides determined requires a donor. Later chromium-51-labelled red corpuscles were introduced, and this replaced phosphorus labelling more and more. The chromium-51 loss amounts to only 5 per cent in the course of the first day and to −1 per cent daily later. By applying labelled chromate, the life-span of the red corpuscles can be determined as well as the corpuscle volume. Furthermore, as chromium-51 emits gamma-rays, we can determine its activity by making use of the very convenient scintillation counter. If we inject 1 millilitre of phosphorus-32- or chromium-51-labelled red corpuscles of an activity of 100 000 units and find after the lapse of 15 minutes or so that 1 milligram of red corpuscles contains 50 activity units, we can conclude that the labelled red corpuscles were diluted by 2 litres of red corpuscles. Thus the red corpuscles content of the circulation amounts to 2 litres.

As it is more convenient to determine the haemoglobin concentration of the blood only, this magnitude and not the haemoglobin content of the blood is determined. In the Donner Laboratory of the University of Berkeley, corpuscle volume and haemoglobin concentration are determined in each case, the latter by the phosphorus-32 method. Thus the total haemoglobin content can in each case be stated. Chromium-51-labelled red corpuscles can also be used in the determination of the total haemoglobin content. When determin-

ing the plasma volume, usually a known amount of iodine-labelled albumin of known activity is injected and the dilution shown by the activity of the labelled albumin determined. Here again the principle of isotope dilution finds application.

ACTIVATION ANALYSIS

We have considered some examples of the application of radioactive indicators in analytical chemistry in which tracers found in nature or produced by bombardment with neutrons or possibly in the cyclotron were applied. We shall now consider an example in which the tracer is produced *in situ* in the sample exposed to neutron bombardment. The first activation analyses were carried out by making use of rare-earth elements produced by Auer von Welsbach, the only person who possessed pure samples of all rare-earth elements before the Second World War. Auer von Welsbach was interested in my hafnium studies and repeatedly invited me to spend some time with him in his castle situated in Carinthia. The by-products of the manufacture of the Auer mantle and of the cerium-iron alloys used to light cigars contained large amounts of the different rare-earth elements. The rough purification of the rare earths was carried out in his factory at Treibach near Auer's castle. He himself carried out the later stages of purification alone, crystallizing the double sulphates of the rare-earth elements. Auer von Welsbach presented me on each of my visits with minute amounts of all the rare-earth elements. One day he was in a generous mood and told me he was willing to present me with larger amounts of one of the rare-earth elements. Without having a special reason for doing so, I chose dysprosium. After the discovery of artificial radioactivity by Frédéric Joliot and Irène Curie, I exposed Auer's dysprosium to a neutron stream emitted by a mixture of 600 milligrams of radium, 400 milli-curies of radon and some beryllium. The exposed dysprosium became excee-dingly active, dysprosium being the element showing the most intense artificial radioactivity. This observation induced me to determine the dysprosium content of an yttrium sample by exposing it to a neutron stream, which was the first activation analysis. About the same time. Professor Luigi Rolla of the University of Florence asked me if I could determine if the 2 kilograms of gadolinium oxide which he had prepared contained some europium. We used to test Rolla's samples by X-ray spectroscopy but having at that date no X-ray spectroscope fitted-up, I decided to investigate Rolla's samples by activation analysis. Fifty milligrams of his various gadolinium fractions were wrapped in a quartz film and placed symmetrically in a paraffin block in the centre of which was the neutron source. The intensity of the latter was not sufficient to produce more than a minor activity in gadolinium and it was the europium atoms which mainly captured the neutrons and formed active europium iso-topes. To obtain quantitative results, we exposed Auer's pure gadolinium oxide with known additions of Auer's pure europium simultaneously with Rolla's samples. All samples were placed at the same distance from the neutron source. The result of the analysis of Rolla's samples is seen in Table I. Rolla's best fraction contained 0.4 per cent and his poorest fraction 0.96 per cent europium oxide.

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TABLE I*

ACTIVATION ANALYSIS OF GADOLINIUM OXIDE

(The sample "Standard" is pure Gd_2O_3 to which 2% of Eu_2O_3 was added.
Samples 1 - 4 represent stages in the purification process carried out by
Professor Rolla)

Samples	count/minutes
"Standard"	125
1	60
2	60
3	30
4	25

* G. Hevesy and H. Levi: "Artificial Activity of Hafnium and Some Other Elements"
Kgl. Danske Vid. Sels. Math-fys. Medd. 15, 11 (1938).

TABLE II

Element	Mass number of the produced isotope	Minimum amount determined after	
		1 day exposure	saturation exposure
Na	24	4×10^{-10}	3×10^{-10}
P	32	3×10^{-8}	7×10^{-10}
K	42	4×10^{-9}	3×10^{-9}
Fe	59	1×10^{-5}	3×10^{-7}
As	76	2×10^{-10}	9×10^{-11}
Sr	81	1×10^{-8}	1×10^{-8}
Ag	108	2×10^{-11}	2×10^{-11}
J	128	1×10^{-10}	1×10^{-10}
La	140	3×10^{-10}	1×10^{-10}
Eu	152	2×10^{-12}	2×10^{-12}
Dy	165	1×10^{-12}	1×10^{-12}
Yb	175	2×10^{-10}	4×10^{-11}
Au	198	4×10^{-11}	1×10^{-11}
Bi	210	4×10^{-7}	5×10^{-8}

Our neutron stream was not sufficient to produce a significant amount of labelled gadolinium, as only 22 per cent of the gadolinium is converted into an active gadolinium isotope (159); 78 per cent of the exposed gadolinium is converted into stable heavier gadolinium isotopes. The absorbing power of gadolinium-158 nuclei is only one fiftieth of that of europium-151. Seaborg, at about the same time, showed the presence of 6 ppm of gallium in iron by activation analysis making use of the mighty deuteron beam of the Berkeley cyclotron.

Whereas in the first determination of europium using activation analysis in 1938, only about 0.01 milligram could be determined by our neutron source, in 1954 2×10^{-4} milligrams could be measured when exposed to a flux of 10^{12} neutrons per cm^2 per second in an uranium reactor.

Table II shows the minimum amount of some elements which can be determined by exposing the sample to a neutron flux of 10^{12} neutrons per cm^2 per second for a day and also until saturation is reached.

Activation analysis has proved to be useful in many cases. A classical example is the determination of whether a fatal poisoning with arsenic was a chronic one or not. Arsenic has an affinity for the hair thread; if different parts of the thread are investigated by activation analysis, all parts should prove to be radioactive in the case of a chronic poisoning, while in the case of a single large dose, mainly a restricted part of the thread will be so, i.e. that grown between the administration of arsenic and death.

If only a small fraction of the isotopes of an element is converted into an active isotope, as for example in the case of gadolinium, it may be of advantage to replace the emission method of analysis by an absorption method. If we wish to know the gadolinium content of a europium oxide sample, we prepare standard samples of pure europium oxide containing one per cent, 5 percent and so on of gadolinium oxide and compare the absorption of a neutron beam in the samples and the sample to be analysed.

Isotopic indicators found an extended application in the field of analytical chemistry. I have restricted myself to mentioning a few applications only, the introduction of which I have had opportunity to follow at close quarters.