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A GLANCE AT THE HISTORY OF NUCLEAR MEDICINE

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The development of nuclear medicine has resulted in several effective routine methods in diagnosis and therapy. There is an ongoing discussion about the future of the activity based on the fast development of ultrasound, CT and MR. In such discussions, it is often forgotten that nuclear medicine is also a dynamic diagnostic tool under continous progress. As seen from this historical review, nuclear medicine has grown from quite simple in vitro tests to very advanced methods to image organ function. This is the result of the development of radiopharmaceuticals and instrumentation. Today, development is moving towards what is called receptor scintigraphy, i.e., the use of radiopharmaceuticals which are very specific to certain diseases, for instance, tumours. Even at present there is no other method for early detection of bone metastases than bone scintigraphy. Also, there is no other method to determine the regional myocardial blood flow both at stress and at rest, than myocardial scintigraphy. Nuclear medicine will remain an important diagnostic tool as long as it employs people with engagement and interest. Such people will also guarantee that the hospital management will supply the activity with funds for the necessary investments.

Nuclear medicine is the use of radioactive tracers generally called radiopharmaceuticals in the study of global and regional function, bloodflow, metabolism and morphology of an organ. By tradition, therapy using unsealed sources is also considered a part of nuclear medicine. Sometimes nuclear medicine is described as a triangle with the patient in the center and the biomedical problem, the radiopharmaceutical and the instruments occupying the three corners.

I once heard Henry Wagner the Nestor of nuclear medicine in USA, saying that positron emission tomography (PET) is a revolutionary method for our understanding of the physiology of the brain. This is certainly true. His statement can, however, be extended to all uses of radioactive tracers in medicine and biology, meaning that much of our current knowledge of physiological and metabolic processes in the body is due to the radioactive tracer method. It has been, and still is, a very important tool in research and clinical practice. Nuclear medicine is one main branch of the tree of methods using radioactive tracers. During the last decades it has grown from an exclusive method to a widespread and important diagnostic modality. The annual frequency of nuclear medicine examinations in developed countries is about 16 examinations/1 000 population (1).

Nuclear medicine is an advanced diagnostic tool which must be handled by a well-educated and trained staff representing different areas of competence: physicians, physicists, pharmacists, engineers and technicians. Its organization differs from country to country. In large countries nuclear medicine is generally a medical speciality while, for example in Sweden, the activity is organized, under radiology, clinical physiology, clinical chemistry, oncology or hospital physics.

Physicists

The discovery of x-rays on November 8 1895, was reported to the French Academy of Science in January 1896. One of its members was the physicist Henri Bec-

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querel at Musée d'Histoire Naturelle in Paris. He had the impression that the new rays were generated from the point of the discharge tube which emitted fluorescent light when it was hit by cathode rays. This gave him the idea that other fluorescent materials might also emit the same type of radiation and he subsequently began a series of experiments in order to investigate this. He used a salt of uranium and potassium and was able to show that, after being exposed to sunlight, this substance emitted radiation which could penetrate black paper and blacken a photographic plate. He reported his findings to the Academy on February 24, 1896 (2). He then intended to repeat his experiments but the sky over Paris was too cloudy for producing an effective excitement of fluorescense. On March 1, he nevertheless developed his photographic plates expecting only a minor blackening, but the blackening was as deep as in his previous experiments. In his report to the Academy on March 2, 1896 he wrote; 'I shall particularly insist on the following fact, which appears to me very important and quite outside the range of the phenomena one might expect to observe. The same crystalline lamellas, placed opposite photographic plates, under the same conditions, separated by the same screen, but shielded from excitation by incident radiation and kept in darkness, still produce the same photographic impression' (3).

Bequerel's discovery inspired several scientists to further research on this new phenomena. Marie and Pierre Curie named it radioactivity and tried to chemically isolate the substance which emitted the radiation. They then discovered two new elements, radium and polonium. Ernest Rutherford at Cavendish Laboratory in Cambridge started his work to dissect the atom. He identified alpha- and betaparticles. Together with F. Soddy he examined the temporal properties of the radioactive decay and the transformation of one element to another or a physically divergent form of the same element; isotopes as Soddy later named them. Rutherford (he supervised 11 future Nobel Prize winners) and co-workers were able to show that the mass of an atom is concentrated in a small nucleus with the electrons occupying orbits around it. This formed the basis of the atom theory proposed by Niels Bohr in 1913.

This was a very dynamic period in physics. Two main theories were formed: the theory of relativity proposed by A. Einstein and the quantum theory with M. Planck as the first in the line of several scientists in this field. The understanding of the structure of the atom and the nucleus subsequently increased. The neutron was discovered by J. Chadwick in 1932 and in 1934 F. Joliot and I. Curie were able to prove the production of an artificial radionuclide, ^{30}P, as a result of bombarding aluminium with neutrons from a radium-beryllium source. 'These experiments give the first chemical proof of artificial transmutation ---', they proudly wrote (4, 5)

George de Hevesy

The possibility to produce artificial radionuclides was something the chemist George de Hevesy had long waited for. In 1911, when working under Rutherford at the Cavendish Laboratory, he developed the idea that a radioactive substance, chemically unseparable from a stable substance, could be used as an indicator of the latter. Together with F. Paneth he used this method to study the solubility of lead salts (6). This was the first application of radioactive tracers. de Hevesy also realized that this method could be used to study biological processes but the natural radionuclides available at this time were all so poisonous that such experiments were rendered impossible. He did, however, conduct one experiment where he observed how an isotope of lead was taken up and distributed in a plant (Vicia faba) (7).

In 1935, de Hevesy came to Niels Bohr's Institute in Copenhagen. His main interest was to find a radionuclide which could be used in biological research. He selected ^{32}P and started a series of experiments where different phophorus compounds were given to animals in order to study the distribution and metabolism of the substances. Together with the Danish physician O. Chievitz, he published the first results in the journal 'Nature', in September 1935 (8). This publication revealed new information about the metabolism of the skeleton. 'The results strongly support the view that the formation of bone is a dynamic process, the bones continuously taking up phosphorus atoms which are partly or wholly lost again and are replaced by other phosphorus atoms.', they wrote.

De Hevesy was awarded the Nobel Prize in chemistry in 1943 and moved that same year to Sweden where he continued his work at Stockholm University. There, he focused primarily on studying the turnover of nucleic acids using ^{32}P as a tracer, until his death in 1966 at the age of 81. With all deference to the other people involved, de Hevesy must be regarded as the father of the radioactive tracer method and hence the father of nuclear medicine. This fact has been recognized by the European Association of Nuclear Medicine which instituted a medal in his memory.

Radiopharmaceuticals

The practical problems of de Hevesy were to obtain enough activity of ^{32}P. This radionuclide is produced by neutron bombardment of sulphur and the only source of neutrons at that time was radium-beryllium where the alpha-particles from radium released neutrons from beryllium. The fluence of neutrons achieved in this way is very limited. However, in 1930 E. Lawrence at the University of California in Berkeley, developed the first cyclotron and at the end of 1933 he had built a machine capable of yielding a beam of 3 MeV deutrons and with an intensity equivalent to enormous quantities of radium in a Ra-Be source.

Neutrons were produced by bombardment of light elements with deutrons. It now became possible to produce radionuclides of nearly all elements in quantities sufficient to allow start of medical and biological research.

Although cyclotrons were soon spread to many countries of the world, their wide-scale use to produce radionuclides for routine medical purposes were still limited. On December 2, 1942, E. Fermi and co-workers achieved the first self-sustained nuclear chain reaction and the construction of the nuclear reactor began. With the reactor, radioactive isotopes could be produced in quantities which were millions of times greater than those which could be produced by cyclotrons at that time. Radionuclides for medical and biological research were now available for general use and the first commercial announcement was published in the June 14, 1946 issue of the journal Science. Of special importance for the start of nuclear medicine in the Nordic countries was the production of radionuclides at Harwell in the UK, which began at the end of 1947. Five shipments to UK hospitals were made that year, this amount increasing to 2 800 in 1951, including shipments to hospitals in the Nordic countries (9).

The most commonly used radionuclides for diagnosis and therapy at that time were ^{32}P, ^{24}Na and ^{131}I. Phosphorus and iodine are still important in radionuclide therapy where now several other radionuclides have been introduced such as ^{89}Sr, ^{90}Y, ^{125}I, ^{153}Sm, ^{186}Re, ^{198}Au (10).

The radionuclide ^{131}I has played an important role in diagnostic nuclear medicine. Not only was it the radionuclide of choice for different examinations of the thyroid but it was also used as a tracer to label different pharmaceuticals. It was produced and identified for the first time in 1938 and almost immediately used on humans. The first report came from Berkeley where Hamilton and Soley measured the uptake of the radionuclide in excised specimens of human thyroid glands (11). Already in 1938, Hertz et al. (12) had produced ^{128}I which was administered to rabbits. They found that the thyroid gland contained about nine times the concentration of the radionuclide found in the liver. From this study they concluded that when strongly active materials are available, the concentration power of the hyperplastic and neoplastic thyroid for radioactive iodine may be of clinical and therapeutic significance (12).

Currently, the most widely used radionuclide in diagnostic nuclear medicine imaging is $^{99}Tc^m$. In 1962, it was proposed as a useful agent by P.V. Harper and co-workers at the Argonne National Laboratory in the USA (13). This radionuclide is a daughter of ^{99}Mo which can be produced by fission or by neutron activation of stable Mo. The separation of $^{99}Tc^m$ from ^{99}Mo was originally achieved by fairly complicated chemical methods and because of its short physical half-life, $^{99}Tc^m$ had to be delivered to hospitals every day. This required a highly efficient transportation system without delays. Later, when the technetium generator was developed, users were able to obtain a daily supply of this radionuclide by a simple elution procedure. The generator, together with the uncomplicated methods for in-house production of radiopharmaceuticals, has made nuclear medicine more widely available, even for small hospitals.

Instrumentation

One of the main reasons for the great success of the radioactive tracer method is the ability to efficiently detect the radionuclide. Until 1949, the only counting device for external detection of a radioactive substance was the Geiger-Müller (GM) tube. Unfortunately, the tube was very insensitive to penetrating gamma-rays from such radionuclides as ^{131}I. Nevertheless, attempts were made to use collimated GM tubes for the study of thyroid function and morphology.

The scintillation effect of ionizing radiation by certain crystals of high density and transparency has been well known since the beginning of this century. Later the photomultiplier tube was developed and this instrument was able to effectively detect the scintillation light and transfer it to an electrical signal. The first scintillation counter for medical use was constructed by B. Cassen et al. at UCLA (14). It utilized a crystal of calcium tungstate and was especially designed for the localization of radioactive iodine in the thyroid. The instrument originally performed well and its effectiveness was further enhanced by the introduction of large sodium iodide crystals and end-windowed photomultiplier tubes. In the following years, a variety of external counting procedures, employing scintillation detectors, were developed ranging from pre-operative localization of brain tumours to determination of cardiac output and kidney function.

A collimated scintillation detector was also used to delineate the morphology of the thyroid gland using point-by-point measurements from a grid with 400 point definition (15). This procedure took hours and was very impractical. Attempts were then made to automate the positioning of the detector which led to the development of the rectilinear scanner by B. Cassen and L. Curtis (16). In Sweden, at NUKAB in Göteborg, Erik Berne and Ulf Johnsson built a rectilinear scanner which was sold worldwide and Lars Jonsson and Inger Ragnhult in Stockholm constructed the first whole body scanner (17). The rectilinear scanner quickly became the standard instrument used in nuclear medicine imaging and remained so for two decades. Its drawback, however, was that the time required to scan a big organ like the lungs or the skeleton, was considerable and that dynamic examinations were impossible. Hence the need for a large stationary detector became obvious. In 1952, H.O. Anger at Donner Laboratory in the USA constructed a pin-hole camera for gamma-rays. With this instrument, an image of the radionuclide distribution

was projected by the collimator on a sodium iodide crystal and the scintillation light was recorded on a photographic film in optical contact with the crystal (18). At the same time S. Johansson and B. Skanse in Malmö, Sweden, constructed a similar camera, using a multiple hole collimator which increased sensitivity (19). The sensitivity of this instrument, however, was still too low for practical use. The breakthrough for the stationary detector came in 1957 when Anger constructed the prototype of the modern gamma camera (20). He replaced the film in his previous construction by an array of photomultiplier tubes. By weighting together the signals from the tubes, he was able to localize the origin of the scintillation process and hence the origin of the registered gamma ray. The position signals were fed into the deflection plates of a cathode ray tube and the single absorption events were successively registered on a photographic film until an image of the radionuclide distribution in the organ had been achieved.

It took a few years before the gamma camera became a widely used instrument. In Sweden, for example, the first camera was installed in 1967 at the University Hospital in Lund 10 years after its original construction. The design, however, has prevailed as modern cameras are still built according to Angers' original principle, although the performance of the camera has improved considerably and during the last decade, digital technology has been introduced into its construction.

The computer has a long tradition in nuclear medicine. It is used not only for advanced image processing and the quantitative analysis of examinations, but also for the reconstruction of tomographic examinations. Tomography in nuclear medicine has its origins in the work by Kuhl & Edwards in USA (21). In Sweden, S. Larsson in Stockholm, contributed to the devolopment of the first clinically useful, tomographic system (22). Also, A. Israelsson wrote the reconstruction algorithms for a PDP 11/34 and it was offered for sale by Nuclear Diagnostics Ltd, in Stockholm.

Diagnostic methods

The different methods used in diagnostic nuclear medicine have changed considerably over the years. At the beginning, they were mainly in vitro type, examinations which included methods like iodine and iron turnover, the determination of blood volume and cardiac output, survival evaluations of circulating erythrocytes and the determination of sodium and potassium space. These methods gradually decreased and disappeared in favour of in vivo, examinations. Originally, these used simple, single detector systems and included methods like the determination of iodine uptake in the thyroid, renography and radiocardiography, and the determination of liver function and blood flow.

The introduction of the rectilinear scanner meant that the distribution of a radiopharmaceutical in an organ could be measured. The first applications of this technique involved thyroid scans and different methods for the localization of tumours. Gradually bone, liver and lung scans, among others, were introduced. Since the introduction of the gamma camera and $^{99}Tc^{m}$, diagnostic nuclear medicine has basically become an imaging technique.

A radionuclide was employed in diagnostic medicine as early as in 1927, when Blumgart & Weiss (23) used ^{214}Bi to measure circulation time from one arm to the other in both normal and abnormal patients. The ensuing report can be regarded as the birth of clinical nuclear medicine. This method was then further developed using ^{24}Na. However, it never became of major clinical significance itself but is the origin of more advanced methods to study circulation. In 1948, Prinzmetal et al. (24) used an external GM-tube over the heart region. After a bolus-injection of ^{24}Na, the count-rate was registered and from this curve, named radiocardiogram, the transit time between right and left ventricles could be determined. Nylin & Celander in Stockholm, used ^{32}P and sampling of arterial blood in their early method to determine cardiac output (25). Later, external measurements were used (26). The method is still in use today, mainly as a tool to quantify intracardiac shunts (27).

Another type of blood flow measurement technique involved merely injecting ^{24}Na directly into a muscle and then measuring its disappearance rate. This method was introduced by Kety (28) and then further developed by Lassen et al. (29) who introduced the concept of using a radioactive, noble gas. This concept is also used in measuring of regional cerebral blood flow, a practice introduced by Ingvar & Lassen (30). Apart from positron emission tomography, it is still the only method to quantitatively measure regional cerebral blood flow. Relative measurements are routinely made with the gamma camera utilizing various substances labelled with $^{99}Tc^{m}$ and used in the diagnosis of dementia and stroke, among others.

Measurements of regional myocardial blood flow is today a very important method in nuclear medicine, used mainly to detect ischemic heart disease. The examination is generally performed both at stress and rest. The origin of this method is Love and co-worker's research in 1954, which showed an uptake of both potassium and rubidium in the myocardium (31). Later Carr et al. (32) were able to scintigraphically detect experimental infarcts in animals using ^{86}Rb and ^{131}Cs. Several radionuclides were tested over the years and the general breakthrough of myocardial scintigraphy came in 1975 when Strauss et al. used ^{201}Tl (33). This method is still in use, but in competition with methods using a number of substances labelled with $^{99}Tc^{m}$.

The blood flow of an organ can be determined by using a radiopharmaceutical, which is extracted by the organ with an efficiency close to 100%. The disappearance rate of the radiopharmaceutical from the blood is a measure of

the organ blood flow. This technique was early used to measure the blood flow in both liver and kidneys. The mechanism behind a high extraction might be physiological, meaning that the uptake of the radiopharmaceutical in the cells of an organ is very effective. This principle is used in the methods for both brain and myocardial scintigraphy described above. The mechanism can also be mechanical, meaning that particles are injected and trapped in the capillary system. This principle is used in perfusion scintigraphy of the lungs, one of the basic examination types in nuclear medicine. The method has its origin in the early 1960s when Taplin et al. (34) produced and tested a macroaggregated human serum albumin labelled with ^{131}I. Iodine was later replaced by $^{99}Tc^{m}$ (35). The particles are trapped in the capillary tree of the lungs and a reduced uptake is equivalent to a reduced perfusion which can be caused by a lung embolus. However, a decreased uptake might appear for other reasons and subsequently the need for a method to study regional ventilation arose. Such a method was introduced in 1965 by Taplin & Poe (36). They used an aerosol which still is the most wideley spread method but for radioactive noble gases like ^{133}Xe which have also been used.

Early diagnostic methods utilizing radiopharmaceuticals were restricted by the limited number of radionuclides available and by the lack of efficient detectors. Still, however, early attemps were made to detect ^{32}P in vivo although it is a pure beta-emitter. Early observations showed an increased uptake of the radionuclide in tumours and Low-Beer et al. (37) made external measurements of superficial breast tumours showing a 25% increased uptake compared with that of surrounding tissues. ^{32}P was also used to localize brain tumours at surgery and to detect skin tumours and intraocular tumours (38–40).

Localization of tumours in vivo have always been a challenge to nuclear medicine and the greatest success has been achieved in the area of bone metastases. After early trials, using ^{32}P and ^{45}Ca, a breakthrough came by the introduction of the gamma-emitting radionuclide ^{85}Sr. Gynning et al. (41) used this radionuclide in external detection of spinal metastases. Cederqvist (42) performed retention studies in patients with and without widespread malignant skeletal disease using a whole body counter. The first scintigraphies were performed by Fleming et al. in 1961 (43). In the middle of the 1960s, several reports had pointed to the fact that bone metastases could be detected by bone scintigraphy several months earlier than with conventional radiological methods. Today, bone scans are still the most common procedure in nuclear medicine. The radiopharmaceuticals used in this procedure are phosphates, diphophonates or similar agents labelled with $^{99}Tc^{m}$, as suggested by Subramanian & McAfee in 1971 (44).

Over a period of several years, brain scintigraphy using $^{99}Tc^{m}$-pertechnetate and liver scintigraphy using $^{99}Tc^{m}$-colloids became very important when diagnosing tumours in these organs. These methods were gradually replaced by CT and ultrasound during the 1980s. However, $^{99}Tc^{m}$-colloids are still used in bone marrow scintigraphy and it is worth mentioning that the first scintigraphy of this kind was made in Stockholm by Engstedt et al. (45). Also different procedures in the diagnosis of different diseases of the thyroid have had their golden era. These procedures have, to a large extent, been replaced by different laboratory tests. As mentioned above, it was early discovered that iodine is absorbed by the thyroid and several diagnostic methods to measure the function of the thyroid were developed, including the uptake test; 24 h collection of urine and different types of hormone analysis. The textbook 'Diagnostic radioisotopes' from 1959 contains 528 references concerning iodine metabolism, thyroid function and diagnostic tests (46). This reveals that the examination of the thyroid was a milestone in the history of nuclear medicine or, more precisely, its development from an exclusive research tool to an important tool in diagnosis. Moreover, it created the need for special instrumentation, such as the scintillation counter, the rectilinear scanner and the gamma-camera as previously mentioned. In Sweden, diagnostic nuclear medicine began with the thyroid in all the university hospitals around 1950 with Bengt Skanse as the pioneer. Important contributions to the development of methods and instruments for diagnosis of thyroid diseases have come from Sweden (17, 47–50).

In 1956, Taplin et al. (51) and Winter (52), used diodrast labelled with ^{131}I for examination of the kidneys. After intravenous injection, the uptake and excretion were studied with external detectors directed to each kidney. This represented the birth of renography, a method which is very common today. Taplin et al. stated that renography had a potential use as a screening test for younger patients with hypertension and for determining the progress of treatment through repeated tests. Diodrast was soon replaced by ^{131}I-hippuran, a substance introduced in 1960 by Nordyke et al. (53). It is extracted effectively by the kidneys both through filtration and by tubular secretion, thereby minimizing the background problem in renography which results in a more precise determination of kidney split function. This radiopharmaceutical and its clinical use, has been carefully examined by G. Magnusson in Stockholm (54). A measure of the kidney function is the glomerulus filtration rate expressed as clearance. It was introduced in the 1920s and has been used in clinical routines for the determination of kidney function in terms of clearance of inulin and urea. The orignal, non-radioactive methods were quite complicated with a continous collection of urine and a constant level of the substance in plasma. Nosslin (55, 56) showed that clearance can be determined from a single injection of a substance followed by sampling of plasma to establish a plasma concentration curve. Bröchner-Mortensen (57) used this concept in his

method to determine the glomerulus filtration rate by using ^{51}Cr-EDTA, a method still in common use.

Radionuclide therapy

In March 1936, Hamilton & Stone in California, employed the first artificially produced radioisotope for therapeutic trials (58). They used ^{24}Na in three patients with leukemia and allied diseases. They also investigated the uptake and excretion of radiosodium in these patients. A few months later J.H. Lawrence at Berkeley initiated the therapeutic use of ^{32}P for the treatment of leukemia and polycythemia vera (59). In the years to follow, several reports on the successful use of ^{32}P in therapy were issued. This method of utilizing radiophosphorus in the treatment of polycythemia vera is still in use. In Sweden, the first report on use of radionuclides in the treatment of leukemia was issued by E. Lindgren in 1944 (60). L.-G. Larsson used ^{32}P in the treatment of mycosis fungoides (61).

Radiophosphorus has been used extensively in both diagnosis and therapy. One important application is colloidal ^{32}P in the treatment of patients with pleural effusion and ascites (62). This kind of intracavitary use of radioactive colloids, mainly ^{198}Au, for palliation treatment of malignant effusion began in 1945 (63). Although radiocolloid instillations have been made in other closed cavities, the primary application is still in the chest and abdomen.

Another use of colloids labelled with ^{32}P, ^{90}Y, ^{198}Au and other radionuclides, is for performance of medical synovectomies. This work began in the early 1960s (64) and the results were promising with an improvement rate of 50-60% (65).

Early works by Hahn et al. (66) and Lawrence et al. (67) revealed that ^{32}P was metabolized by the skeleton, especially by neoplastic tissues. Hence the concept of treatment of bone metastases arose. This method dates back to the early 1950s and in particular the work by Storaasli et al. (68) and that by Maxfield et al. (69). They used ^{32}P which unfortunately had the disadvantage of a high absorbed dose to bone marrow. This led to the introduction of ^{89}Sr which gave the same pain relief as ^{32}P but without marrow suppression (70, 71). The use of ^{89}Sr is still an important routine methods for treatment of pain from bone metastases, especially in patients with prostatic carcinoma.

The most extensive use of unsealed sources has been in the treatment of the thyroid with radioactive iodine. Already in 1941, Hertz & Robert (72) used ^{130}I in the treatment of a patient with hyperthyroidism. They administered only 1 mCi and observed no effect. Therefore they increased the activity to 16 mCi and treated 29 patients with this dose. They concluded that the treatment was effective in 80% of the cases (72, 73). With the introduction of ^{131}I the therapy developed (74). The uptake measurement and scintigraphic imaging made it possible to make an individual dosage of the radionuclide meaning an increased accuracy in the treatment. This method is still the method of choice today in the treatment of hyperthyroidism.

Early experiments using radioactive iodine in the treatment of thyroid cancer were also performed (75). Although the majority of thyroid carcinomas can be removed surgically, it is often uncertain afterwards whether or not the resection will be complete and if local or distant metastases are present. In these cases, treatment with ^{131}I can be used as a supplement. In 1943, Frantz et al. (76) treated a child who had had a total thyroidectomy. They found a good uptake in a metastases in the right pharyngeal wall and noted that an effective ^{131}I therapy of metastases might well depend upon the removal of the functional thyroid gland. Seidlin et al. (72) then demonstrated that metastatic carcinoma of the thyroid can be successfully treated with radioactive iodine, provided of course, that the lesion accumulates iodine.

REFERENCES

1. UNSCEAR 1994. Sources and effects of ionizing radiation. UNSCEAR 1994 Report to the general assembly with scientific annexes. United Nations Scientific Committee on the Effect of Atomic Radiation, New York: United Nations, 1994.
2. Becquerel H. Sur les radiations émises par phosphorescence. Comp Rend Acad Sci 1896; 122: 420–1.
3. Becquerel H. Sur les radiations invisible émises par les corps phosphorescent. Comp Rend Acad Sci 1896; 122: 501–3.
4. Curie I, Joliot F. Radioactivité-séparation chemique des nouveaux radioelements emetteurs d'Électron positifs. Comp Rend Acad Sci 1934; 198: 254.
5. Joliot F, Curie I. Artificial production of a new kind of radioelements. Nature 1934; 133: 201 2.
6. Hevesy G, Paneth F. Die Löslichkeit des Bleisulfids und Bleichchromats. Z Anorg Chem 1913; 82: 323.
7. Hevesy G. III. The absorption and translocation of lead by plants. Biochem J 1923; 17: 439.
8. Chiewitz O, de Hevesy G. Radioactive indicators in the study of phosphorus metabolism in rats. Nature 1935; 136: 754–5.
9. Mallard J, Trott NG. Some aspects of the history of nuclear medicine in the United Kingdom. Semin Nucl Med 1979; IX: 203–17.
10. Hoefnagel CA. Radionuclide therapy revisited. Eur J Nucl Med 1991; 18: 408–31.
11. Hamilton JG, Soley MH. Studies in iodine metabolism by use of a new radioactive isotope of iodine. Am J Physiol 1939; 127: 557–72.
12. Hertz S, Roberts A, Evans RD. Radioactive iodine as an indicator in the study of thyroid physiology. Proc Soc Exp Biol Med 1938; 38: 510.
13. Harper PV, Andros G, Lathrop K, Siemens W, Weiss L. Technetium-99 as a biological tracer. J Nucl Med 1962; 3: 209.
14. Cassen B, Curtis L, Reed CA. A sensitive directional gamma-ray detector. Nucleonics 1950; 5–6: 78.
15. Allen H, Libby R, Cassen B. The scintillation counter in clinical studies of human thyroid physiology using I-131. J Clin Endocrinol Metab 1951; 11: 492.
16. Cassen B, Curtis L, Reed A, Libby RL. Instrumentation for I-131 use in medical studies. Nucleonics 1951; 9: 46–9.

17. Jonsson L, Ragnhult I, Larsson L-G. A scanning apparatus for the localization of gamma-emitting isotopes in vivo. Acta Radiol 1957; 47: 217–28.
18. Anger HO. Use of gamma-ray pinhole camera for in-vivo studies. Nature 1952; 170: 200.
19. Johansson SAE, Skanse B. A photographic method of determining the distribution of radioactive material in vivo. Acta Radiol 1953; 39: 317–22.
20. Anger HO. A new instrument for mapping gamma-ray emitters. Biol Med Quart Rep 1957; UCRL–3653: 38.
21. Kuhl DE, Edwards RQ. Image separation radioisotope scanning. Radiology 1963; 80: 653–62.
22. Larsson SA. Gamma camera emission tomography. Development and properties of a multi-sectional emission computed tomography system. Acta Radiol 1980; (Suppl 363).
23. Blumgart HL, Weiss S. Studies on the velocity of blood flow. J Clin Invest 1927; 4: 15–31.
24. Prinzmetal M, Corday E, Bergman HC, et al. Radiocardiography. A new method for studying the blood flow through the chambers of the heart in human beings. Science 1948; 108: 340–2.
25. Nylin G, Celander H. Determination of blood volume in the heart and lungs and the cardiac output through the injection of radiophosphorus. Circulation 1950; 1: 76–83.
26. Veall N, Pearson JD, Hanley T, Lowes AE. A method for the determination of cardiac output preliminary report. In: Proceedings of the Second Radioisotope Conference. Vol I: Medical and Physiological Applications. New York: Academic Press, 1954: 183–92.
27. Parker JA, Treves S. Radionuclide detection and quantitation of intracardiac shunts and shunts between the great vessels. Prog Cardiovasc Dis 1977; 20: 121–50.
28. Kety SS. Measurements of regional circulation by the local clearance of radioactive sodium. Am Heart J 1949; 38: 321–8.
29. Lassen NA, Lindbjerg H, Munck O. Measurements of blood flow through skeletal muscle by intramuscular injection of Xe-133. Lancet 1964; 1: 686–9.
30. Ingvar DH, Lassen NA. Quantitative determination of regional cerebral blood flow in man. Lancet 1961; 2: 806–7.
31. Love WD, Romney RB, Burch GE. A comparison of the distribution of potassium and exchangeable rubidium in the organs of the dog using rubidium-86. Cir Res 1954; 2: 112.
32. Carr EA Jr, Bierwaltes WH, Patno ME, et al. The detection of experimental myocardial infarcts by photoscanning. Am Heart J 1962; 64: 650.
33. Strauss HW, Harrison K, Langee JK, et al. Thallium-201 for myocardial imaging. Relation of thallium-201 to regional myocardial perfusion. Circulation 1975; 51: 641–5.
34. Taplin GV, Johnson DE, Dore EK, et al. Lung photoscans with macroaggregates of human serum radioalbumin. Experimental basis and initial clinical trials. Health Phys 1964; 10: 1219–27.
35. Taplin GV, Johnson DE, Kennedy JC et al. Aggregated albumin labeled with various radioisotopes. Radioactive pharmaceuticals, USAEC, TID 1966.
36. Taplin GV, Poe ND. A dual lung-scanning technic for evaluation of pulmonary function. Radiology 1965; 85: 365.
37. Low-Beer BVA, Bell HG, McCorkle HJ, Stone RS. Measurement of radioactive phosphorus in breast tumors in situ: possible diagnostic procedures: preliminary report. Radiology 1946; 47: 492–3.
38. Bauer FK, Steffen CG. Radioactive phosphorus in the diagnosis of skin tumors. JAMA 1955; 158: 563–5.
39. Krohmer JS, Thomas CI, Storaasli JP, et al. Detection of intraocular tumors with the use of radioactive phosphorus. Radiology 1953; 61: 916–21.
40. Selverstone B, Solomon AK, Sweet WH. Location of brain tumours by means of radioactive phosphorus. JAMA 1949; 140: 277–8.
41. Gynning I, Langeland P, Lindberg S, Waldeskog B. Localization with Sr-85 of spinal metastasis in mammary cancer and changes in uptake after hormone and roentgen therapy. A preliminary report. Acta Radiol 1961; 55: 119–28.
42. Cederqvist E. Clinical application of whole body counting of Sr-85 and Ca-47 in patients with and without widespread malignant skeletal disease. Acta Radiol 1964; (Suppl 232).
43. Fleming WH, McIlraith JD, King ER. Photoscanning of bone lesions utilizing Sr-85. Radiology 1961; 77: 635.
44. Subramanian G, McAfee JG. A new complex of Tc99m for skeletal imaging. Radiology 1971; 99: 192–6.
45. Engstedt L, Franzén S, Jonsson L, Larsson L-G. In vivo localization of colloidal Au-198 intravenously injected in polycythemia vera. Acta Radiol 1958; 49: 66–71.
46. Owen CA. Diagnostic radioisotopes. Springfield, Illinois: C.C. Thomas Publisher, 1959.
47. Egmark A, Larsson LG, Liljestrand Å, Ragnhult I. Iodine-concentrating thyroid carcinomas. Acta Radiol 1953; 39: 423–33.
48. Einhorn J. Studies on the effect of thyrotropic hormone on the thyroid function in man. Acta Radiol 1959; (Suppl 160).
49. Larsson L-G. Studies on radioiodine treatment of thyrotoxicosis with special reference to the behaviour of the radioiodine tracer tests. Acta Radiol 1955; (Suppl 126).
50. Skanse B. Radioactive iodine in the diagnosis of thyroid disease. Acta Med Scand 1949; (Suppl 235).
51. Taplin GV, Meredith OM, Kade H, Winter CC. The radioisotope renogram. J Lab Clin Med 1956; 48: 886–901.
52. Winter CC. A clinical study of a new renal function test: The radioactive diodrast renogram. J Urol 1956; 76: 182–96.
53. Nordyke R, Tubis M, Bladh WH. Use of radioiodinated hippuran for individual kidney function tests. J Lab Clin Med 1960; 56: 438–45.
54. Magnusson G. Kidney function studies with ^{131}I-tagged sodium ortho-isodohippurate. Acta Med Scand 1962; (Suppl 378).
55. Nosslin B. Mathematical model of plasma protein turnover determined with ^{131}I-labelled protein. In: Andersen SB. Metabolism of human gamma-globulin. Oxford: Blackwell, 1964: 115–20.
56. Nosslin B. Determination of clearance and distribution volume with the single injection technique. Acta Med Scand 1965; 179 (Suppl 442): 97–101.
57. Bröchner-Mortensen J. A simple method for the determination of glomerular filtration rate. Scand J Clin Lab Invest 1972; 30: 271.
58. Hamilton JG, Stone RS. The intravenous and intraduodenal administration of radiosodium. Radiology 1937; 28: 178.
59. Lawrence JH. Nuclear physics and therapy; preliminary report on a new method for the treatment of leukemia and polycythemia. Radiology 1940; 35: 51–60.
60. Lindgren E. Versuche mit Radioaktiven Isotopen bei Leukämibehandlung. Acta Radiol 1944; 25: 614–24.
61. Larsson L-G. Internal treatment of mycosis fungoides with P–32. Acta Radiol 1952; 37: 577–82.
62. Jacobs ML. Radioactive collodial chromic phosphate to control pleural effusion of ascites. JAMA 1958; 166: 6.
63. Müller JH. Weitere Entwicklung der Therapie von Peritonealcarcinosen bei Ovarialcarcinom mit künstlische Radioaktivität (Au-198). Gynaecologia 1950; 129: 298.

64. Ansell BM, Crook A, Mallard J, et al. Evaluation of intra-articular colloid gold Au-198 in the treatment of persistent knee effusions. Am Rheum Dis 1963; 22: 435–9.
65. Ahlberg A, Mikulowski P, Odelberg-Johnson O. Intra-articular injection of radioactive gold in treatment of chronic synovial effusion in the knee. Acta Rheumatol Scand 1969; 15: 81–9.
66. Hahn LO, Hevesy GC, Lundsgaard EQ. The circulation of phosphorus in the body revealed by application of radioactive phosphorus as indicator. Biochemistry 1937; 31: 1705–7.
67. Lawrence JH, Tuttle LW, Scott KG, et al. Studies on neoplasms with the aid of radioactive phosphorus. I. The total phosphorus metabolism of normal and leukemic mice. J Clin Invest 1940; 19: 267–71.
68. Storaasli JP, King RI, Krieger H, et al. Palliations of osseous metastases from breast carcinoma with radioactive phosphorus alone and in combination with adrenalectomy. Radiology 1961; 76: 422–9.
69. Maxfield JR, Maxfield JG, Maxfield WS. Use of radioactive phosphorus and testosterone in metastatic bone lesions from breast and prostate. South Med J 1958; 51: 320–8.
70. Firusian N, Mellin P, Schmidt CG. Results of Sr-89 therapy in patients with carcinoma of the prostate and incurable pain from bone metastases: preliminary report. J Urol 1976; 116: 764–8.
71. Schmidt CG, Firusian N. Sr-89 in the treatment of incurable pain in patient with neoplastic osseous infiltrations. Int J Clinic Pharmacol 1974; 93: 199–205.
72. Hertz S, Roberts A. Application of radioactive iodine in the therapy of Graves' disease. J Clin Invest 1942; 21: 624.
73. Hertz S, Roberts A. Radioactive iodine in the study of thyroid physiology VII. The use of radioactive iodine therapy in hyperthyriodism. JAMA 1946; 131: 81.
74. Hamilton JG, Soley MH. Studies in iodine metabolism of the thyroid gland in situ by the use of radioiodine in normal subjects and in patients with various types of goiter. Am J Physiol 1940–41; 131: 135.
75. Keston AS, Ball RP, Frantz VK, et al. Storage of radioactive iodine in a metastasis from thyroid carcinoma. Science 1942; 95: 362.
76. Frantz VK, Ball RP, Keston AS, et al. Thyroid carcinoma with metastases, studies with radioactive iodine. Ann Surg 1944; 119: 668–89.
77. Seidlin SM, Marinelli LD, Oshry E. Radioactive iodine therapy effect on functioning metastases of adenocarcinomas of the thyroid. JAMA 1946; 132: 838–47.