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MEDICAL RADIOISOTOPES PRODUCTION WITHOUT A NUCLEAR REACTOR

The vast majority of the public thinks that research reactors, such as the High Flux Reactor (HFR) in Petten, the Netherlands, are essential for the supply of medical radioisotopes. And indeed these nuclear reactors are currently producing the vast majority of the isotopes. The nuclear industries like to maintain this widespread misunderstanding to justify their right to exist. A brief look in the history of nuclear medicine learns that all medical radioisotopes were originally manufactured by another type of production.

(710/1.) Laka Foundation – On May 22, a research report was published on the alternatives for reactor-based production of medical isotopes: "*Medical Radioisotopes Production Without A Nuclear Reactor*", written by Henk van der Keur of the Laka Foundation. The report tries to find an answer to the key question: Is it possible to ban the use of research reactors for the production of medical radioisotopes? It will make clear that the nuclear industry is using the production of medical isotopes as public relation for nuclear research reactors. The production of medical isotopes is seen as the sole purpose of the planned replacement of the Dutch High-Flux reactor by the Pallas-reactor, although 50% percent of reactor-time will be used for nuclear related research. All medical-isotopes now produced in reactors can be produced alternatively or can be replaced by isotopes which can be produced other than in a nuclear reactor.

Isotopes are naturally occurring or are artificially made. The first ones are often stable, while the last ones are unstable or radioactive. There have been characterized about 1600 isotopes, either stable or unstable (radioactive). Radioactive isotopes or radioisotopes have numerous applications in medicine, agriculture, industry and fundamental research. Though most isotopes have no practical value, dozens of isotopes have valuable applications. At present there are up to 200 radioisotopes used on a regular basis, and most of them are produced artificially.

Until 2007 there was an almost uninterrupted supply of cheap subsidized reactor-produced isotopes, there was no need to search for alternatives. Since January 2007, there has been at least six periods of serious disruption to supplies. Only in Canada these disruptions were followed by serious debates on how to secure the domestic supply of radiopharmaceuticals in the nearby future and the future. The development of accelerator-based production of medical isotopes has always been thwarted in favor of the production with nuclear reactors. Policy-makers are opting for research reactors, because they offer large scale production of medical isotopes. The continued disruptions, however, have proven that the reactor method is not safe and secure. And why should the isotopes production be dependent on a few worldwide monopolists? Cyclotrons offer the possibility to produce hospital-based medical isotopes.

Chapter 1

INTRODUCTION

Medical imaging is one of the fastest growing disciplines in medicine. The development of innovative new imaging modalities and radiopharmaceuticals has improved the ability to study biological structures and functions in health and disease, and continues to contribute to the evolution of medical care. Besides the routine use of X-rays, the most common imaging techniques in current clinical practice are: *computed tomography* (CT or CAT), *magnetic resonance imaging* (MRI), *ultrasound* (US), *planar scintigraphy (gamma camera)* and *single photon emission computed tomography* (SPECT). The use of *Positron emission tomography* (PET) is less common, but is growing fast. CT and MRI scanners, ultrasound units and gamma cameras are now an essential part of clinical practice. PET and magnetic resonance spectroscopy (MRS) are also increasingly used in the management of patients with cancer and neurological disorders. Planar scintigraphy, CT, SPECT and PET make use of ionizing radiation, and except for CT, these nuclear imaging modalities make use of medical radioisotopes. SPECT/CT and PET/CT perform better than SPECT and PET respectively. Therefore the share of these hybrid modalities is increasing rapidly.

Artificially made radioisotopes, among which those for medical use, are mainly produced by research reactors. Currently more than 80% of the medical radioisotopes are produced by research reactors. The remaining isotopes are made by particle accelerators, mostly with circular accelerators (cyclotrons) and sometimes with linear accelerators (linacs), or by other methods. Production of medical isotopes is used by the nuclear industry as public relation for nuclear research reactors. The production of medical isotopes is seen as the sole purpose of the planned replacement of the Dutch High Flux reactor by the Pallas reactor, although 50 percent of reactor-time will be used for nuclear related research. Actually, such research reactors are not necessary at all for the production of isotopes. After an intense debate in Canada the Canadian government recently decided to cancel the plan for the construction of a new research reactor and to opt for isotopes production with particle accelerators. They have learnt from their mistakes in the past and have chosen for innovation and modernization. Canada should be a shining example for the rest of the world.

Radioisotopes production with cyclotrons offers many advantages over a nuclear reactor. Firstly, the volume of radioactive waste produced by cyclotrons is far less and much less hazardous than the radioactive waste of research reactors. Secondly, the production is decentralized. Cyclotrons are located hospital-based, by which the delivery of pharmaceuticals to patients is much more secured. In addition the risk of transport accidents is practically zero. Thirdly, there are no risks due to nuclear-power accidents, because there is no need for controlled chain reactions. Fourthly, there is no nuclear proliferation risk.

This report is answering the key question: Is it possible to ban the use of research reactors for the production of medical radioisotopes? A recent bulletin of the World Nuclear Association (WNA) on nuclear medicine stated: "Over 10,000 hospitals worldwide use radioisotopes in medicine, and about 90% of the procedures are for diagnosis. The most common radioisotope used in diagnosis is technetium-99m (in technical jargon: ^{99m}Tc), with some 30 million procedures per year, accounting for 80% of all nuclear medicine procedures worldwide."[1] Other sources mentions the figure 80-85%[2], and the figure of 90% of all diagnostic procedures in Europe in 2008[3] (European Association of Nuclear Medicine). Today, technetium-99m (^{99m}Tc) can be manufactured easily by using cyclotrons. Besides technetium-99m there are also other popular medical isotopes that can be made with cyclotrons. At the same time radiopharmaceuticals used with PET oust increasingly the ^{99m}Tc radiopharmaceuticals currently in use. In addition, there are other accelerator-based isotopes with energies that are similar to the energies of reactor-produced isotopes, currently in use in nuclear medicine. A few isotopes that can't be made now by accelerators can be made by sub-critical systems, such as accelerator-driven systems (ADS). The rapid development of new accelerator-based isotopes can make the use of such systems redundant in the near future.

[1] Radioisotopes in Medicine. 16 April 2010: http://www.world-nuclear.org/info/inf55.html

[2] Kahn, Laura H.; The potential dangers in medical isotope production. Bulletin of the Atomic Scientists, 16 March 2008: http://www.isotopeworld.com/filestore/Danger%20Medical%20Isotope%20pdf.pdf

[3] Public Health - Radioisotopes for Medical Use http://ec.europa.eu/health/ph_threats/radioisotopes/radioisotopes_en.htm

Chapter 2

THE EMERGENCE AND DEVELOPMENT OF NUCLEAR MEDICINE

The vast majority of the public thinks that research reactors, such as the *High Flux Reactor (HFR)* in Petten, the Netherlands, are essential for the supply of medical radioisotopes. And indeed these nuclear reactors are currently producing the vast majority of the isotopes. The nuclear industries like to maintain this widespread misunderstanding to justify their right to exist. A brief look in the history of nuclear medicine learns that all medical radioisotopes were originally manufactured by another type of production. The first medical applications of radioisotopes paralleled the development of the nuclear physics instruments which all these isotopes produced: the *(charged) particle accelerators*. Currently, these instruments are mistakenly purely seen as tools in fundamental scientific research.

2.1 Original production of radioisotopes

Tracer principal

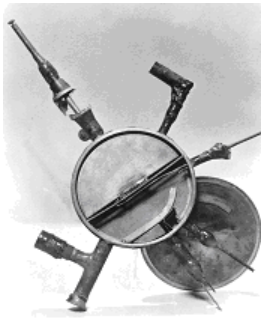
Radiopharmaceuticals are used as radioactive tracers for the diagnosis and treatment of patients. The Hungarian chemist George Charles de Hevesy, born as Hevesy György, published the first paper on the radioactive tracer concept in 1913. He coined the term *radioindicator* or *radiotracer* and introduced the *tracer principle* in biomedical sciences. An important characteristic of a tracer is that it can facilitate the study of components of a homeostatic system without disturbing their function. In 1924, the tracer concept paved the way for the use of radioisotopes as diagnostic tools. In 1927, the US physicians Hermann Blumgart and Soma Weiss injected solutions of bismuth-214 (^{214}Bi) into the veins of men to study the velocity of blood.

Particle accelerator

After the discoveries of the cyclotron by Ernest Lawrence in 1931 and artificial radioactivity by Irène Curie and Jean-Frédéric Joliot in 1934, it was possible to make practically every imaginable radioisotope for use in diagnostics or in therapy. Isotopes such as iodine-131 (^{131}I), phosphorus-32 (^{32}P) and cobalt-60 (^{60}Co) are already used in diagnostics and therapy since the mid-1930s.[4] By bombarding an aluminum sheet with particles emitted by polonium Curie and Joliot created for the first time a radioactive element, which they baptized radio-phosphorus. Coupled with the Geiger counter's detection capabilities, their discovery markedly expanded the range of possible radioisotopes for clinical tracer studies. Enrico Fermi produced a whole range of radioisotopes, including phosphorus-32 (^{32}P). Soon ^{32}P was employed for the first time to treat a patient with leukemia. Ernest Lawrence recognized the medical potential of radioisotopes. His brother, John, a hematologist, helped researched the field's potential and established and administered the therapeutic procedures. In 1936 he treated a 28-year-old leukemia patient using ^{32}P produced in one of his brother's cyclotrons. It was for the first time that a radioisotope had been used in the treatment of a disease, marking the birth of nuclear medicine.

In 1938, Emilio Segre discovered technetium-99m (^{99m}Tc), and thyroid physiology was studied by using radioactive iodine. It was discovered that thyroid accumulated radioiodine (^{131}I). Consequently it was soon realized that ^{131}I could be used to study abnormal thyroid metabolism in patients with goiter and hyperthyroidism. More specifically, in patients with thyroid cancer, distant metastases were identified by scanning the whole body with the Geiger counter. The names *radioisotope scanning* and *atomic medicine* were introduced to describe the medical field's use of radioisotopes for the purpose of diagnosis and therapy. Strontium-89 (^{89}Sr), another compound that localizes in the bones is currently used to treat pain in patients whose cancer has spread to their bones, was first evaluated in 1939.[5] All of these radioisotopes are now considered as 'typical reactor-produced isotopes'

(The first successful cyclotron)



[4] From Radioisotopes to Medical Imaging, History of Nuclear Medicine Written at Berkeley, 9 September 1996. http://www.lbl.gov/Science-Articles/Archive/nuclear-med-history.html
Lawrence And His Laboratory - A Historian's View of the Lawrence Years: Ch2 The Headmaster and His School. Lawrence Berkeley National Laboratory, 1981. http://www.lbl.gov/Science-Articles/Research-Review/Magazine/1981/81fchp2.html

[5] Chemistry Explained - Nuclear Medicine: http://www.chemistryexplained.com/Ne-Nu/Nuclear-Medicine.html

The first commercial medical cyclotron was installed in 1941 at Washington University, St. Louis, where radioactive isotopes of phosphorus, iron, arsenic and sulfur were produced. Soon there hadn't been enough cyclotron capacity to fulfill the rising demand of isotopes. Civilian use of a military nuclear reactor provided relief to the producers of pharmaceuticals. The Manhattan Project – the US-led project to develop the first atomic bomb - resulted in an unprecedented expansion of radiation research and expertise, as well as its diagnostic and therapeutic application in nuclear medicine, including human experimentation. As a byproduct of nuclear reactor development, radioisotopes came to abound. As a result of this most radioisotopes of medical interest began to be produced in a nuclear reactor during World War II. Especially in the Oak Ridge reactor, which was constructed under the secrecy of the Manhattan Project. To protect this secrecy, the ^{32}P produced by the reactor had to appear as if it had been produced by a cyclotron. Thus, ^{32}P was sent from Oak Ridge to the cyclotron group at the University of California at Berkeley, from which it was distributed to the medical centers. The shortage of radioisotopes ended in 1945, when isotopes became widely available for research and medical use, including reactor-produced ^{131}I from Oak Ridge. Globally, particle accelerators produced the vast majority of radioisotopes with medical applications until the 1950s when other countries followed the US by using reactor-based isotopes.

2.2 The rise of reactor-produced radioisotopes

After the war, the US continued its atomic research in a series of national laboratories, among them Los Alamos and Oak Ridge. These labs were supervised by the then Atomic Energy Commission (AEC), a governmental agency to coordinate the military, economic, political, and scientific work in atomic energy. The main mission of the AEC was promoting the military use of nuclear material, but "giving atomic energy a peaceful, civilian image" was also part of it. Including the promotion of research, among which radiobiology and nuclear medicine. Immediately after the war, radioisotopes flooded the laboratories and hospitals. In 1946, as part of the Isotope Distribution Program of the AEC, the Oak Ridge Reactor (see archive picture below) began delivering radioisotopes to hospitals and universities nationwide. In 1948 isotopes for biomedical research, cancer diagnostics and therapy even became free of charge, which can be considered as an early forerunner of the Atoms for Peace Campaign in the early 1950s aimed to promote the 'the peaceful use of nuclear energy'. The rest of the western world followed this change in isotopes production. Entirely prospectless the particle accelerators tasted defeat in the competition with the subsidized nuclear reactors.[6]

The cyclotron-based radioisotopes production for medical applications revived a little in the 1950s, after the discovery that thallium-201 (^{201}Tl) could be used as an ideal tracer for detecting myocardial perfusion. Thallous chloride labeled with ^{201}Tl remains the gold standard for measuring cardiac blood flow despite the availability of technetium-99m myocardial perfusion agents.

(Oak Ridge National Laboratory – early 1950s)

[6] Rheinberger, Hans-Jörg; Putting Isotopes To Work: Liquid Scintillation Counters, 1950-1970. Max-Planck-Institut für Wissenschaftsgeschichte, Berlin 1999. pp.4-5 http://edoc.mpg.de/get.epl?fid=3199&did=46724&ver=0

2.3 Nuclear imaging modalities

Gamma camera

The era of nuclear medicine, as a diagnostic specialty began following the discovery of the gamma camera based on the principle of scintillation counting, first introduced by Hal Anger in 1958. Since then, nuclear medicine has dramatically changed our view of looking at disease by providing images of regional radiotracer distributions and biochemical functions. Over the last five decades, a number of radiopharmaceuticals have also been designed and developed to image the structure and function of many organs and tissues.

Molybdenum-99/Technetium-99m (^{99}Mo/^{99m}Tc) generators

In 1959 the U.S. Brookhaven National Laboratory (BNL) started to develop a generator to produce technetium-99m from the reactor fissionable product molybdenum-99, which has a much longer half-life. The first ^{99m}Tc radiotracers were developed at the University of Chicago in 1964. Between 1963 and 1966, the interest in technetium grew as its numerous applications as a radiotracer and diagnostic tool began to be described in publications. By 1966, BNL was unable to cope with the demand for ^{99}Mo/^{99m}Tc generators. BNL withdrew from production and distribution in favor of commercial generators. The first commercial generator was produced by Nuclear Consultants, Inc. of St. Louis, later taken over by Mallinckrodt (Covidien), and Union Carbide Nuclear Corporation, New York.[7]

Computed Tomography (CT)

CT is a medical imaging method employing tomography created by computer processing. The CT-scan was originally known as the *EMI-scan* as it was developed at a research branch of EMI, a company best known today for its music and recording business. It was later known as computed axial tomography (CAT or CT scan) and body section röntgenography. Although the term *computed tomography* could be used to describe positron emission tomography and single photon emission computed tomography, in practice it usually refers to the computation of tomography from X-ray images. The initial use of CT for applications in radiological diagnostics during the 1970s sparked a revolution in the field of medical engineering. In 1972, the first EMI-Scanner was used to scan a patient's brain. CT provided diagnostic radiology with better insight into the pathogenesis of the body, thereby increasing the chances of recovery.[8]

Positron Emission Tomography (PET)

Another major breakthrough in the history of nuclear medicine arrived with the preparation of fluorodeoxyglucose (FDG) labeled with fluorine-18 (^{18}F) in the mid-1970s. Use of ^{18}F-FDG for studying the glucose metabolism lead to the development of the imaging modality *positron emission tomography* (PET). The use of ^{18}F-FDG in combination with a PET-camera produced images of an excellent quality of the brains and the heart for studying aberrations, and the detection of metastases of tumors. Subsequently a large number of other ^{18}F-labeled radiopharmaceuticals were developed and the use of new isotopes grows fast. PET scans are performed to detect cancer; determine whether a cancer has spread in the body; assess the effectiveness of a treatment plan, such as cancer therapy; determine if a cancer has returned after treatment; determine blood flow to the heart muscle; determine the effects of a heart attack, or myocardial infarction, on areas of the heart; identify areas of the heart muscle that would benefit from a procedure such as angioplasty or coronary artery bypass surgery (in combination with a myocardial perfusion scan); evaluate brain abnormalities, such as tumors, memory disorders and seizures and other central nervous system disorders; and to map normal human brain and heart function.[9]

Single Photon Emission Computed Tomography (SPECT)

At the end of the 1970s single photon emission tomography (SPECT) was introduced. Its development parallels the development of PET. SPECT images are produced from multiple 2D projections by rotating one or more gamma cameras around the body. Reconstruction using methods similar to those used in X-ray CT provides 3D data sets allowing the tracer biodistribution to be displayed in orthogonal planes. SPECT uses gamma-emitting radioisotopes, such as ^{99m}Tc and the cyclotron-produced indium-111 (^{111}In) and iodine-123 (^{123}I). The advantages of SPECT over planar scintigraphy can be seen in the improvement of contrast between regions of different function, better spatial localisation, improved detection of abnormal function and, importantly, greatly improved quantification.[10]

Hybrids of CT, PET, SPECT and MRI

The last decade has seen the development of hybrid imaging technologies. PET or SPECT are combined

[7] The Technetium-99m Generator: http://www.bnl.gov/bnlweb/history/tc-99m.asp

[8] Bartlett, Christopher A.; EMI and the CT Scanner [A] and B] www.blackwellpublishing.com/grant/docs/10EMI.pdf

[9] Positron Emission Tomography – Computed Tomography (PET/CT); Radiology Info http://www.radiologyinfo.org/en/info.cfm?PG=pet

[10] What is SPECT?: http://www.spect.net/: Nuclear Technology Review 2007, IAEA. p.61

with X-ray computed tomography (CT). Experts agree that PET/CT and SPECT/CT are superior techniques over stand-alone PET and SPECT in terms of diagnostic accuracy. Insiders expect that these hybrid imaging technologies will become the gold standard for conventional scintigraphy. Hybrid cameras combining PET and MRI have already been introduced. They also prospect the development of new hybrid forms for a certain organ or body part. These systems will offer the virtually unlimited potential of simultaneously acquiring morphologic, functional, and molecular information about the living human body.[11]

2.4 Drawbacks of using PET, SPECT and especially (devices combined with) CT

Despite the major improvements in nuclear medicine by using modalities such as CT, PET and SPECT, investigations in the US uncovered that 20 to 50% of these high-tech scans have been unnecessary, because they offer no support by making a diagnosis.[12] The U.S. National Cancer Institute reports alarming figures on the high radiation exposure of patients. It projects 29,000 excess cancers from the 72 million CT scans that Americans got in 2007 alone. Nearly 15,000 of those cancers could be fatal.[13]

An investigation by the US National Council for Radiation Protection and Measurements shows that frequent use of radioisotopes at one patient can result in a too high radiations exposure. It uncovered that the average dose has been increased from 3,6 millisievert (mSv) in the early 1980s to 6,2 mSv in 2006. The average dose per person is an average over the population of the United States.[14] Apparently the enthusiasm to use these modern modalities has gone too far, which reminds to the widespread use of X-ray equipment in the 1950s.

By the end of February 2010, the U.S. Food and Drug Administration announced a federal program to prevent unnecessary radiation exposure from nuclear imaging devices and new safety requirements for manufacturers of CT scans. Medical doctors are urged to think twice before ordering such scans in order to weigh the risk and the benefit. According to estimates of David Brenner, director of Columbia University's Center for Radiological Research in New York, 20 million adults and one million children are being irradiated unnecessarily and up to 2% of all cancers in the U.S. at present may be caused by radiation from CT scans.[15] The American Society for Radiation Oncology (ASTRO) issued a six-point plan that has to improve safety and quality in using CT and other nuclear imaging modalities and reduce the chances of medical errors.[16] So far, there are no figures known about the situation in Europe.

Though CT produces images with far greater clarity and detail than regular X-ray exams, it has been estimated that the average radiation dose of one CT scan is equal to roughly 500 chest X-rays. An international study, conducted by the IAEA and published in April 2010 has shown that some countries are over-exposing children to radiation when performing CT scans. These children are receiving adult-sized radiation doses, although experts have warned against the practice for over a decade. An additional problem in developing countries is that the available CT machines are older models without the automatic exposure controls found in modern equipment. This function can detect the thickness of the section of the patient´s body that is being scanned and can therefore optimize the level of radiation dose, avoiding unnecessary exposure. The IAEA has started a program to reduce unnecessary child radiation doses.[17]

Meanwhile newer CT technology has been developed to reduce a patient's exposure to excess radiation. Patients who got a type of heart CT scan called coronary angiography received 91% less radiation

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[11] Nuclear Medicine 2020: What Will the Landscape Look Like?
http://www.molecularimaging.net/index.php?option=com_articles&view=article&id=17661:nuclear-medicine-2020-what-will-the-landscape-look-like

[12] Where Can $700 Billion In Waste Be Cut Annually From The U.S. Healthcare System? Robert Kelley, Thomson Reuters, October 2009.
http://www.ncrponline.org/PDFs/Thomson_Reuters_White_Paper_on_Healthcare_Waste.pdf

[13] Radiation From CT Scans May Raise Cancer Risk, 15 December 2009
http://www.npr.org/templates/story/story.php?storyId=121436092&ft=1&f=1007

[14] Medical Radiation Exposure of the U.S. Population Greatly Increased Since the Early 1980s, NCRP Press Release, 3 March 2009.
http://www.ncrponline.org/Press_Rel/Rept_160_Press_Release.pdf
People Exposed to More Radiation from Medical Exams, Health Physics Society, 9 March 2009.
http://hps.org/media/documents/NCRP_Report-People_Exposed_to_More_Radiation_from_Medical_Exams_9Mar.pdf

[15] Radiation Risks Prompt Push to Curb CT Scans. Wall Street Journal, 2 March 2010.
http://online.wsj.com/article/SB10001424052748704299804575095502744095926.html

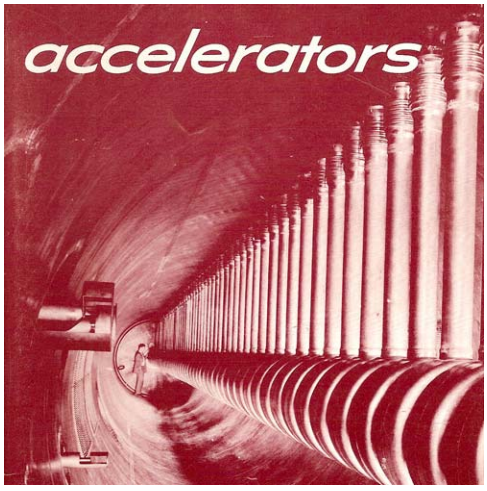
[16] Medical Group Urges New Rules on Radiation. New York Times, February 4, 2010.
http://www.nytimes.com/2010/02/05/health/05radiation-.html

[17] IAEA Aims to Reduce Unnecessary Child Radiation Doses - New Study Shows Global Variation in Dose Levels for Child CT Scans. IAEA, 23 April 2010:http://www.iaea.org/NewsCenter/News/2010/childctscans.html

than those who were scanned with a traditional CT scanner. Although in the U.S. heart CTs only accounted for 2.3 million out of 65 to 70 million CT scans performed in 2006, they are worrisome because they deliver high radiation doses.[18]

2.5 Methods in radiotherapy

Brachytherapy is used for primary cancer treatment, for bone pain palliation, and for radiosynovectomy, used for patients that are suffering from joint pain. In cancer treatment the radionuclides are placed very close to or inside the tumor. During the therapy, controlled doses of high-energy radiation, usually X-rays, destroy cancer cells in the affected area. The radiation source is usually sealed in a small holder called an implant. Implants may be in the form of thin wires, plastic tubes called catheters, ribbons, capsules, or seeds. The implant is put directly into the body. Brachytherapy dates back to the time before the discovery of the cyclotron when natural radioisotopes, such as radium-226 (^{226}Ra), were used in the treatment. Currently, common radionuclides are iridium-192 (^{192}Ir), yttrium-90 (^{90}Y), iodine-125 (^{125}I) and palladium-103 (^{103}Pd).[19]



(accelerator used in fundamental scientific research)

[18] Newer heart CTs deliver far less radiation. Reuters, 24 February 2010

[19] Flynn A et al. (2005). "Isotopes and delivery systems for brachytherapy". in Hoskin P, Coyle C. Radiotherapy in practice: brachytherapy. New York: Oxford University Press.

Chapter 3

MEDICAL RADIOISOTOPES & APPLICATIONS

Over 10,000 hospitals worldwide use radioisotopes in medicine. The vast majority of these isotopes is produced by research reactors. Currently, there are 232 operational research reactors in 56 IAEA member states.[20] Most of these reactors are used for nuclear research, including the ones involved in isotope production. Only 78 out of these 232 research reactors in 41 IAEA member states are used for isotope production.[21] Twelve research reactors, distributed over 11 member states, are temporary shutdown[22], of which three of them are involved in isotope production.[23] The IAEA database mentions that seven research reactors are under construction or planned in 6 member states.[24] It is not clear how many of these are involved in isotope production. More than half of the research reactors involved in isotope production (43 out of 78) is 40 years old or older.[41]

There are about 40 neutron-activated radioisotopes and five fission product ones made in reactors. By 1970, 90% of the radioisotopes in the US, the largest consumer of medical radioisotopes, utilized either iodine-131 (^{131}I), cobalt-60 (^{60}Co), or technetium-99m (^{99m}Tc). ^{60}Co was used for over 4 million therapeutic irradiations a year, ^{131}I for diagnosis and treatment more than 2 million times a year, and ^{99m}Tc in nearly one million annual diagnostic procedures. Today the statistics are somewhat different.[25]

Technetium-99m (^{99m}Tc) is now the worldwide workhorse of nuclear medicine. In the next 40 years there will be steady increase in the demand for cyclotron-produced PET isotopes in the worldwide production of radiopharmaceuticals.

Cyclotron-produced radionuclides are generally prepared by bombarding stable target material (either a solid, liquid, or gas) with protons and are therefore proton-rich, decaying by β+-emission. These radionuclides have applications for diagnostic imaging with planar scintigraphy, PET and SPECT. Different cyclotron models for the energy range 10-12 MeV with moderate beam intensity are used for production of carbon-11 (^{11}C), nitrogen-13 (^{13}N), oxygen-15 (^{15}O) and fluorine-18 (^{18}F) isotopes widely applied in PET. The search for new and more effective isotopes continues until today. The share of fluorine-18 (^{18}F) in diagnostic imaging is estimated at 10% of the nearly 25 to 30 million procedures performed in 2006.[26] ^{18}F-FDG is a versatile radiopharmaceutical with major applications in oncology, neurology, and cardiology.

3.1 Radioisotopes used in imaging

Radioisotopes used in cancer imaging

Of the many different radionuclides used in diagnostic procedures, only a few are valuable in diagnosing cancer. PET/CT is currently accepted to be the most accurate way to stage and monitor many types of cancer. It is used routinely in detecting tumors of thyroid and primary or metastatic tumors of the bone, brain and liver or spleen. Globally, the vast majority of these investigations are performed using the glucose analogue, ^{18}F-FDG. This radiotracer allows cancers to be seen as 'hot spots' on the PET scan. ^{18}F-FDG PET is emerging as a useful tool in the treatment of breast, colorectal, esophageal, head and neck, lung, pancreatic, and thyroid cancer; lymphoma, melanoma, and sarcoma; and unknown primary tumor. Gallium-68 (^{68}Ga) has been used experimentally in the staging of lymphoma and shows a great deal of promise in bone scanning.[27]

[20] http://www-naweb.iaea.org/napc/physics/research_reactors/database/RR%20Data%20Base/datasets/category/status_operational_reactors.html

[21] http://www-naweb.iaea.org/napc/physics/research_reactors/database/RR%20Data%20Base/datasets/utilization/isotope_prod.html

[22] http://www-naweb.iaea.org/napc/physics/research_reactors/database/RR%20Data%20Base/datasets/category/status_temp_shutdown_reactors.html

[23] http://www-naweb.iaea.org/napc/physics/research_reactors/database/RR%20Data%20Base/datasets/utilization/isotope_prod_list.html

[24] http://www-naweb.iaea.org/napc/physics/research_reactors/database/RR%20Data%20Base/datasets/category/status_reactors_construction.html

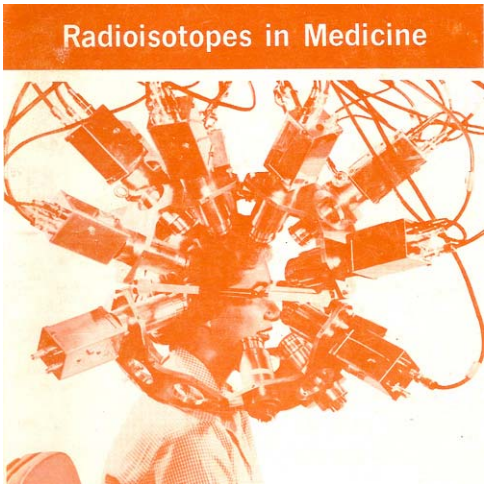
[25] Prof. G.T. Seaborg - Hundred Years of X-rays and Radioactivity (RON-BEC-100) http://www.rca.iaea.org/regional/newFiles/news.html

[26] Nuclear Technology Review 2008, IAEA. pp.39-40

[27] Putzer, Daniel et al.; Bone Metastases in Patients with Neuroendocrine Tumor: ^{68}Ga-DOTA-Tyr3-Octreotide PET in Comparison to CT and Bone Scintigraphy. Journal of Nuclear Medicine Vol. 50 No. 8 1214-1221

Though PET and PET/CT imaging is becoming a dominant modality in cancer imaging, SPECT isotopes, such as technetium-99 (^{99m}Tc) and iodine-123 (^{123}I) are more common for use in cancer imaging. Other isotopes used in cancer imaging are: chromium-51 (^{51}Cr), gold-198 (^{198}Au), indium-113m (^{113m}In), iodine-125 (^{125}I), iodine-131 (^{131}I), mercury-197 (^{197}Hg), mercury-203 (^{203}Hg), selenium-75 (^{75}Se), and Ytterbium-169 (^{169}Yb). Except ^{123}I, all of these radioisotopes are currently produced by research reactors.

Radioisotopes used in cardiac imaging
It is thought that PET imaging may be able to overcome the limitations of the currently used perfusion tracers thallium-201 (^{201}Tl) and technetium-99m (^{99}mTc) in SPECT. Gallium-68 (^{68}Ga) and copper-64 (^{64}Cu) are named as potentially attractive PET tracers for this purpose.[28] Other perfusion agents are: ^{11}C (in CO_2), ^{15}O, ^{13}N (in NH_3) and rubidium-82 (^{82}Rb). Thallium-201 (^{201}Tl), used in cardiac scintigraphy and SPECT, is also used for diagnosis of other heart conditions such as heart muscle death and for location of low-grade lymphomas.



(Radioisotopes used in brain imaging -picture: Understanding the Atom Series, US Atomic Energy Commission, 1966)

Carbon-11 (^{11}C), nitrogen-13 (^{13}N), oxygen-15 (^{15}O) and fluorine-18 (^{18}F) are used in PET for studying brain physiology and pathology, in particular for localizing epileptic focus, and in dementia, psychiatry and neuropharmacology studies. The most widely used radioisotope in brain imaging is ^{99m}Tc (SPECT).

[28] Jain, Diwakar et al; Developing a new PET myocardial perfusion tracer. Journal of Nuclear Cardiology Volume 16, Number 5 689-690/ October, 2009

Radioisotopes used in thyroid imaging
Thyroid imaging tests are used to diagnose or monitor thyroid conditions such as hyperthyroidism, thyroid nodules, thyroid cancer, enlarged thyroid gland (goiter) and thyroiditis. These tests can help a physician to determine the most effective treatment approach for a patient's condition. Types of thyroid imaging tests include isotope imaging with PET and SPECT. PET uses iodine-124 (^{124}I), gallium-68 (^{68}Ga) and fluorine-18 (^{18}F) and shows better results than the more commonly used gamma camera with iodine-131 (^{131}I) or indium-111 (^{111}In) and SPECT with ^{201}Tl and ^{131}I.[29] The iodine-isotopes ^{123}I and ^{131}I remain the most frequently used radionuclides for thyroid imaging in the diagnosis and treatment of well-differentiated thyroid carcinomas (WDTC), which account for almost 90% of thyroid cancers. Although ^{131}I is superior to ^{201}Tl in the detection of lung metastasis, ^{201}Tl may detect metastases not visualized with ^{131}I, and the sensitivity of planar ^{201}Tl may be improved with SPECT from 60 to 85% sensitivity. Imaging with ^{201}Tl has been of value when ^{131}I scans are negative in the presence of known thyroid cancer. ^{201}I has been shown to be useful in patients with WDTC and elevated thyroglobulin levels, despite a negative ^{131}I scan.[30]

Radioisotopes used in renal imaging
There are two types of commonly used scintigraphies to assess the kidney function. Cortical Renal Scintigraphy, an exam used to measure and evaluate the functioning kidney tissue, and Diuretic Renal Scintigraphy, an exam used to detect blockages in the kidney. For these purposes and renal SPECT imaging ^{99m}Tc is the most widely used radioisotope.

The main advantage of PET is that images provide quantitative information on tracer kinetics. Kinetic parameters that correlate with biologically defined processes can be calculated for the entire renal cortex or as pixel-based parametric images. Renal PET studies can be classified as functional (metabolic) imaging studies. Such as determinations of renal blood flow studies with ^{15}O labeled water, ^{13}N labeled ammonia, ^{64}Cu and ^{82}Rb pharmaceuticals. Other isotopes used in renal function imaging are: ^{55}Co and ^{68}Ga.[31]

[29] Phan, Ha T. T. et al.; The diagnostic value of ^{124}I-PET in patients with differentiated thyroid cancer. Eur J Nucl Med Mol Imaging. 2008 May; 35(5): 958–965.
[30] Avram, Anca M. et al.; Alternative Thyroid Imaging. Thyroid Cancer - A Comprehensive Guide to Clinical Management. Humana Press 2007. p.35
[31] Prigent, Alain, and Piepsz, Amy; Functional Imaging in Nephro-Urology. Taylor & Francis, 2005.

3.2 Therapeutic radioisotopes

Therapeutic radiopharmaceuticals in brachytherapy are used for primary cancer treatment or targeted cancer therapy, bone pain palliation and radiosynovectomie. Primary cancer treatment make use of low-dose rate and high-dose rate radionuclides. The low-dose rate isotopes used are: cesium-131 (^{131}Cs), iodine-125 (^{125}I) and Palladium-103 (^{103}Pd). High-dose rate isotopes are: iridium-192 (^{192}Ir), yttrium-90 (^{90}Y), strontium-90 (^{90}Sr) and cesium-137 (^{137}Cs). Pain treatment in palliative care focuses on pain from skeletal metastases of cancer patients who have developed metastasis in bones in the advanced stage of their diseases. Radioisotopes used in this treatment are: strontium-89 (^{89}Sr), samarium-153 (^{153}Sm) and rhenium-186/188 (^{186}Re/^{188}Re) and yttrium-90 (^{90}Y).
Radiosynovectomie is a technique used for patients that are suffering from joint pain. The therapeutic radiopharmaceutical is delivered into the interior of joints that is lubricated by fluid, as in the case of rheumatoid arthritis. Beta-emitting radiolabelled colloids are widely used for this purpose. These radiopharmaceuticals use among others phosphorus-32 (^{32}P), yttrium-90 (^{90}Y), samarium-153 (^{153}Sm), holmium-166 (^{166}Ho), erbium-169 (^{169}Er), and rhenium-186 (^{186}Re). The radiation properties of each radioisotope determine their respective use and applicability for the joint size. Lutetium-177 (^{177}Lu) is a recent and promising isotope in bone pain palliation. ^{177}Lu is also used in targeted cancer therapy. The shorter radius of penetration than ^{90}Y makes ^{177}Lu also an ideal candidate for radioimmunotherapy for smaller, soft tumors. ^{177}Lu is projected to become as important as iodine-131 (^{131}I), the second most used medical radioisotope. Several countries have already begun or are planning medium to large scale production of this radioisotope.[32]

Cancer treatment with radioimmunotherapy and PET

^{68}Ga-PET is not only employed for imaging in the management of neuroendocrine tumors and neural crest tumors, but also for therapeutic use, where it complements present radiologic and scintigraphic procedures. Diagnosis and radiotherapy treatment planning for meningiomas (the second most common primary tumor of the central nervous system) in pertinent clinical setting is another potential use of ^{68}Ga-PET. Therefore, current experience tends to open a new horizon for the clinical utility of ^{68}Ga-PET imaging in future.[33]

Immuno-PET as a quantitative imaging procedure before or concomitant with radioimmunotherapy is an attractive option to improve confirmation of tumor targeting and especially assessment of radiation dose delivery to both tumor and normal tissues. Immuno-PET combines the high resolution and quantitative aspects of PET with the high specificity and selectivity of monoclonal antibodies. This makes immuno-PET an attractive imaging modality for tumor detection. Moreover, immuno-PET has the potential to supersede gamma-camera imaging in combination with radioimmunotherapy, because it enables the sensitive confirmation of tumor targeting and a more reliable estimation of radiation dose delivery to both tumor and normal tissues. Because PET is believed to be superior to SPECT with respect to quantification, several PET radioisotopes have been suggested as substitutes for gamma-emitting radionuclides used in radioimmunoscintigraphy. Theoretically, this could enable easy conversion from a SPECT to a PET procedure. Examples of PET/SPECT radioisotope pairs are ^{94m}Tc/^{99m}Tc, ^{67}Ga/^{68}Ga, and ^{124}I/^{123}I, and examples of PET/radioimmunotherapy radioisotope pairs are ^{64}Cu/^{67}Cu, ^{86}Y/^{90}Y, and ^{124}I/^{131}I.[34] ^{68}Ga can be produced – such as ^{99m}Tc - from a generator system with the parent radionuclide Germanium-68. ^{68}Ge has a long half-life of 271 days which allows the production of long-lived, potentially very cost-effective generator systems. ^{67}Ga en ^{68}Ga have the same medical applications, whereas ^{67}Ga is used with SPECT/CT and ^{68}Ga with PET/CT.

Other therapies

There are also other internal therapies with radionuclides for relieving pain of secondary cancers in the bone. For example a pharmaceutical of samarium-153 (^{153}Sm) is injected into a vein and distributes throughout the body. It lodges in areas where cancer has invaded the bone. It emits beta particles which kill the nearby cancer cells. It is commonly used in lung cancer, prostate cancer, breast cancer, and osteosarcoma.

A method known as *peptide receptor radionuclide therapy* (PRRT) involves the development and use of radiolabelled peptides as molecular vectors for targeted therapy. When labeled with the ^{90}Y and ^{177}Lu, the most frequently used isotopes, peptide molecules have the potential to destroy receptor-expressing tumors.[35]

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[32] Nuclear Technology Review 2009, IAEA. p.45

[33] Khan, M. et al.; Clinical indications for Gallium-68 positron emission tomography imaging. European Journal of Surgical Oncology (EJSO), Volume 35, Issue 6, Pages 561-567.

[34] Verel, PhD., Iris et al.; The Promise of Immuno-PET in Radioimmunotherapy. Journal of Nuclear Medicine (2005) Vol. 46 No. 1 (Suppl) 164S-17 http://jnm.snmjournals.org/cgi/content/full/46/1_suppl/164S

[35] de Jong, PhD, Marion; Combination Radionuclide Therapy Using ^{177}Lu- and ^{90}Y-Labeled Somatostatin

Other radioisotopes used in medicine

Bismuth-213 (^{213}Bi)

^{213}Bi is used for targeted alpha therapy, especially in treatments of cancers, including leukemia.

Chromium-51 (^{51}Cr)

^{51}Cr is used to label red blood cells and quantify gastrointestinal protein loss. Sodium Chromate is indicated for use in determining red blood cell volume or mass, studying red blood cell survival time (in conditions such as hemolytic anemia), and evaluating blood loss. Another ^{51}Cr pharmaceutical is indicated for the determination of glomerular filtration rate in the assessment of renal function.

Copper-64 (^{64}Cu)

^{64}Cu is used to study genetic diseases affecting copper metabolism, such as Wilson's and Menke's diseases which are caused by genetical disorders affecting the metabolism of copper in the body. In Wilson disease, copper builds up in the liver, brain, eyes, and other organs. Over time, high copper levels can cause life-threatening organ damage. Menke's disease primarily affects male infants. Symptoms include floppy muscle tone, seizures, and failure to thrive.[36] The isotope is also used for PET imaging of tumors, and therapy and is considered for routine production

Indium-111 (^{111}In)

^{111}In is used for specialized diagnostic studies, for example brain studies, infection and colon transit studies. Other applications include the labeling of platelets for thrombus detection, labeled leukocytes (type of white blood cells) for localization of inflammation and abscesses, as well as leukocyte kinetics.[37]

Krypton-81m (^{81m}Kr)

^{81m}Kr from rubidium-81 (^{81}Rb): ^{81m}Kr gas can yield functional images of pulmonary ventilation, e.g. in asthmatic patients, and for the early diagnosis of lung diseases and function.

Strontium-82/Rubidium-82 ($^{82}Sr/^{82}Rb$)

^{82}Sr is used as the mother isotope in a generator to produce ^{82}Rb which is a convenient PET agent in myocardial perfusion imaging. ^{82}Rb chloride is used in heart imaging (see images below). It is rapidly taken up by heart muscle cells, and therefore can be used to identify regions of heart muscle that are receiving poor blood flow in a technique called PET perfusion imaging.[38] ^{82}Rb behaves like ^{201}Tl and is a highly promising alternative for ^{201}Tl or ^{99m}Tc SPECT imaging.

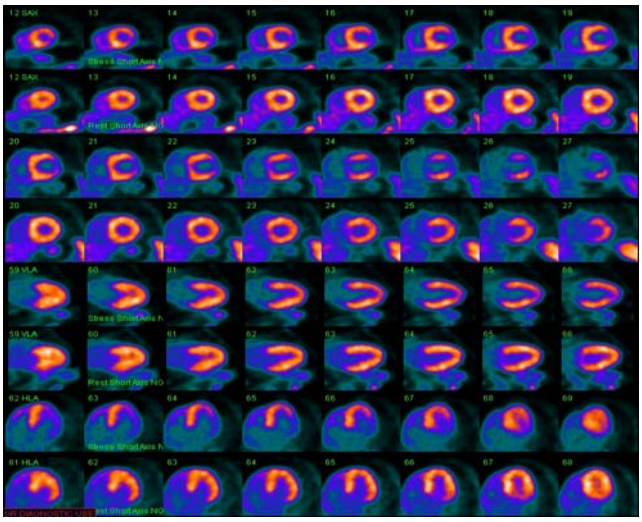
Zinc-65 (^{65}Zn)

^{65}Zn is used in brain cancer imaging and is considered as a tumor suppressor agent in prostate cancer. It is also used as a tracer in studies of zinc metabolism.[39]

Xenon-133 (^{133}Xe)

^{133}Xe is used for pulmonary (lung) ventilation studies.

General Source:
Radioisotopes in Medicine (October 2009), WNA
http://www.world-nuclear.org/info/inf55.html



Analogs. Journal of Nuclear Medicine Vol. 46 No. 1 (Suppl) 13S-17S. http://jnm.snmjournals.org/cgi/content/full/46/1_suppl/13S

[36] Wilson Disease - http://digestive.niddk.nih.gov/ddiseases/pubs/wilson/ NINDS Menkes Disease Information Page - http://www.ninds.nih.gov/disorders/menkes/menkes.htm

[37] In-111 Fact Sheet, MDS Nordion: www.mdsnordion.com/documents/products/In-111_Can.pdf

[38] Rubidium-82 chloride: http://en.wikipedia.org/wiki/Rubidium-82_chloride

[39] Costello, Leslie C., and Franklin, Renty B.; The clinical relevance of the metabolism of prostate cancer; zinc and tumor suppression: connecting the dots. Mol Cancer. 2006; 5: 17. Published online 2006 May 15. doi: 10.1186/1476-4598-5-17. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1481516/

Chapter 4

REACTOR-BASED RADIOISOTOPES PRODUCED BY CYCLOTRONS

It is often claimed by the nuclear industries that reactor-produced radionuclides can be only made by research reactors. A closer look at the production methods, however, learns that this assertion is not tenable. This chapter discusses the production of reactor-based isotopes with particle accelerators, cyclotron-produced isotopes as an alternative for reactor-produced isotopes and other alternatives. The last paragraph highlights the advantages of cyclotrons.

The most commonly used reactor produced isotopes in medical applications are technetium-99m (^{99m}Tc) [decay product of the fission product molybdenum-99 (^{99}Mo)], iodine-131 (^{131}I), phosphorus-32 (^{32}P), chromium-51 (^{51}Cr), strontium-89 (^{89}Sr), samarium-153 (^{153}Sm), rhenium-186 (^{186}Re) and lutetium-177 (^{177}Lu). Therefore these radioisotopes and some other isotopes are discussed here. About 20% of medical applications use radioisotopes such as such as the cyclotron-based ^{201}Tl, ^{111}In, ^{67}Ga, ^{123} I, ^{81m}Kr [parent isotope: ^{81}Rb], and reactor-based ^{131}I and ^{133}Xe. The use of ^{201}Tl for cardiac studies and ^{123} I for thyroid studies is widespread.[40]

4.1 Accelerator production methods for commonly used reactor-based radioisotopes

Technetium-99m (^{99}Tc)

After the continued disruptions in the supply of technetium-99m and other radioisotopes in the past years, Canada commissioned a group of experts to find ways for a more secure supply of radioisotopes. This *Expert Review Panel on Medical Isotope Production* presented its findings at the end of November 2009. Different methods of isotopes production with accelerators, for the production of ^{99}Mo and direct production of ^{99m}Tc, are currently being investigated in Canada. The Expert Review Panel considers direct production of ^{99m}Tc with cyclotrons as the most promising technique and recommends to support a research and development program for cyclotron-based ^{99m}Tc production. The two linear accelerator options for the production of ^{99m}Tc have limited prospects for multi-purpose use, according to the experts. Nonetheless, as a hedge against the risk of failure of other options, the panel recommends a modest R&D investment in the linac technology based on molybdenum-100 transmutation since the projected economics appear better, and it largely avoids nuclear waste management issues. In addition the panel recommends "investments in PET technology to reduce the demand for ^{99m}Tc now and over the longer term, which would reduce the impact of future shortages of reactor-produced isotopes."

The panel's preferred cyclotron option is based on bombarding enriched ^{100}Mo targets with protons to produce ^{99m}Tc according to the charged particle reaction ^{100}Mo(p,2n)^{99m}Tc. This is the only option in which ^{99m}Tc is produced directly without first generating ^{99}Mo. The cyclotron option is considered to be the timeliest option. The panel expects that commercial production of ^{99m}Tc could begin between 2011 and 2014.[41]

Despite the panel's reserved attitude regarding the use of linacs, earlier tests with the linac method they have chosen show good results. In 1998, researchers from Kharkov, Ukraine, published their results on ^{99}Mo production by targeting ^{100}Mo with an energetic electron beam produced by the linac according to the charged particle reaction ^{100}Mo(γ,n)^{99}Mo. They concluded: "[..] the proposed technique has the promise of returning very high profits in a not too-distant future."[42]

Canada's accelerator laboratory TRIUMF has formed a consortium with the Canadian medical isotope supplier MDS Nordion to study the feasibility of making ^{99}Mo in a linear accelerator. This method include irradiating a natural uranium target by a highly intense photon beam to create ^{99}Mo. Construction of the facility at TRIUMF is scheduled to start in 2010 with tests slated for 2013. MDS Nordion and TRIUMF already collaborate on the production of other medical isotopes using cyclotron accelerators.[43]

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[40] Beneficial Uses and Production of Radioisotopes, 2004 Update. NEA/IAEA Joint Publication. OECD 2005. Industrial Applications and Chemisty Section Areas of Activities in Radioisotopes and Radiation Technology, IAEA. http://www-naweb.iaea.org/napc/iachem/areas_of_activities.asp

[41] Report of the Canadian Expert Review Panel on Medical Isotope Production, 30 November 2009. http://nrcan.gc.ca/eneene/sources/uranuc/pdf/panrep-rapexp-eng.pdf
http://nrcan.gc.ca/eneene/sources/uranuc/mediso-eng.php

[42] Uvarov, V.L. et al.; Electron Accelerator's Production Of Technetium-99m for Nuclear Medicine National Science Center Kharkov Institute of Physics & Technology, Kharkov, 1998, Ukraine. http://accelconf.web.cern.ch/accelconf/pac97/papers/pdf/7P112.PDF

[43] Accelerator lab targets medical isotopes, 28 April 2009: http://physicsworld.com/cws/article/news/38860

Another non-reactor method under development is the proton-driven fission neutron source for the production of fission ^{99}Mo as proposed by IBA, a Belgian producer of cyclotrons and one of the market leaders. The IBA proposal is based on a 150 MeV, up to 2 mA cyclotron driving a sub-critical intense neutron source, generating thermal neutron fluxes similar in intensity to those of nuclear reactors used for the production of ^{99}Mo.[44] Such accelerator-driven systems (ADS) can be used in the transition to charged particle accelerator-based isotopes production. The sub-critical ADS produces less waste than critical (research) reactors. Linacs and cyclotrons, however, produce much less waste than ADS. By making a choice for non-reactor production of radioisotopes the use of ADS is temporarily needed to fill the gap in the transition to the production of medical isotopes with charged particle accelerators.

Iodine-131 (^{131}I)

Seaborg and Jack Livingood bombarded tellurium with deuterons in the Berkeley Lab's 37-inch cyclotron, creating ^{131}I in the 1930s. Currently most of the ^{131}I is produced by a reactor. Just like ^{99}Mo it is a fission product of uranium-235. In states such as India ^{131}I is still routinely made with cyclotrons by irradiating tellurium (Te), either as metallic or tellurium dioxide (TeO_2). A recent publication describes a new and simple method of separation of ^{131}I from Te material, generating no or little amount of liquid radioactive waste as compared to the wet distillation technique where a large volume of radioactive and toxic waste generates.[45] Apart from that iodine-123 (^{123}I) appears to be a better diagnostic imaging agent than ^{131}I for diagnosis of thyroid function.[46] The cyclotron produced ^{123}I is therefore increasingly used in thyroid therapy. Studies have shown that ^{99m}Tc is a better option than the use of ^{131}I for the treatment of various renal disorders.[47] A radiopharmaceutical of ^{123}I has better results in therapy for relapsed neuroblastoma than ^{131}I.[48] In addition PET isotopes will replace the use of ^{131}I more and more.

Phosphorus-32 (^{32}P)

^{32}P was one of the first radioisotopes produced with cyclotrons, before the production of reactor-produced isotopes. The ^{32}P was prepared in substantial amounts in the cyclotron of Berkeley Laboratory by bombardment of red phosphorus with deuterons.[49] Besides production with a cyclotron, it can be also produced by linacs.[50]

Strontium-89 (^{89}Sr)

^{89}Sr is just like ^{32}P one of the first radioisotopes used in nuclear medicine. It was produced at the cyclotron and already in 1940 applied to cure prostate metastases in bone. It is still used in palliative therapy of bone metastases.[51] A number of

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[44] Cohilis, P. and Jongen, Y.; High Beam Intensities for Cyclotron-based Radioisotope Production Ion Beam Applications s.a. (IBA), Chemin du Cyclotron 3, B-1348 Louvain-la-Neuve, Belgium (paper from 1996) www.cern.ch/accelconf/e96/PAPERS/THPG/THP075G.PDF

[45] Chattopadhyay, Sankha; A new method of separation of I-131 from tellurium material using a charcoal column. J Nucl Med. 2009; 50 (Supplement 2):1886 http://jnumedmtg.snmjournals.org/cgi/content/meeting_abstract/50/2_MeetingAbstracts/1886

[46] Andó, L.; Pure iodine-123 production by small cyclotron for medical use. Journal of Radioanalytical and Nuclear Chemistry. Volume 146, Number 3 / October, 1990 http://www.springerlink.com/content/u061101072522wx0/ Mandel, S.J. et al.; Superiority of iodine-123 compared with iodine-131 scanning for thyroid remnants in patients with differentiated thyroid cancer. Clin Nucl Med. 2001 Jan;26(1):6-9. http://www.ncbi.nlm.nih.gov/pubmed/11139058 Urhan, M.; Iodine-123 as a diagnostic imaging agent in differentiated thyroid carcinoma: a comparison with iodine-131 post-treatment scanning and serum thyroglobulin measurement. Eur J Nucl Med Mol Imaging - 01-JUL-2007; 34(7): 1012-7 http://www.mdconsult.com/das/citation/body/170946602-2/jorg=journal&source=MI&sp=19963034&sid=0/N/19963034/1.html?issn=

[47] Kabasakal, L.; Clinical comparison of Technetium-99m-EC, Technetium-99m-MAG3 and iodine-131-OIH in renal disorders. The Journal of nuclear medicine. 1995, vol. 36, no2, pp. 224-228 (32 ref.)

[48] Taggart, Denah R. et al; Comparison of Iodine-123 Metaiodobenzylguanidine (MIBG) Scan and [18F]Fluorodeoxyglucose Positron Emission Tomography to Evaluate Response After Iodine-131 MIBG Therapy for Relapsed Neuroblastoma. Journal of Clinical Oncology, Vol 27, No 32 (November 10), 2009: pp. 5343-5349 Veenendaal, Liesbeth M. et al.; Liver metastases of neuroendocrine tumours; early reduction of tumour load to improve life expectancy. World Journal of Surgical Oncology 2006, 4:35

[49] Cohn, Waldo E.; The Early Use of Artificial Radioactive Isotopes. J. Biol. Chem. 123, 185–198 (1938) www.jbc.org/content/277/45/e33.full.pdf

[50] Proceedings of EPAC 2000, Vienna, Austria: Linear Electron Accelerator For the Medical Isotopes Production. Kharkov 2 GeV Linac Team, Kharkov, Ukraine accelconf.web.cern.ch/AccelConf/e00/PAPERS/WEP2B12.pdf

[51] Adloff, P. et al.; One Hundred Years after the Discovery of Radioactivity. R. Oldenbourg Verlag, München, 1996. p.250 Nair, Narendra; Relative Efficacy of 32Pand 89Sr in Palliation in Skeletal Metastases. The Journal Of Nuclear Medicine Vol. 40 No. 2 February 1999. http://jnm.snmjournals.org/cgi/reprint/40/2/256.pdf

publications show that cyclotron-produced ^{89}Sr can be made in large amounts with a cyclotron.[52]

Samarium-153 (^{153}Sm)

^{153}Sm can be also made with alfa-beam irradiation in a cyclotron according to the charged particle reaction ^{150}Nd(α,n)^{153}Sm. In a 2007 publication researchers concluded that the reaction would lead to sufficient yield of the no-carrier-added product, provided a highly enriched target is used.[53]

Rhenium-186 (^{186}Re)

^{186}Re is a newer product for the relief of cancer-induced bone pain and is used as an alternative for ^{153}Sm.[54] It can be also produced by a cyclotron according to the charged particle reaction ^{186}W(p,n) ^{186}Re. It is one of the two important therapeutic isotopes of rhenium. The advantage over ^{188}Re is the longer half-life, the advantage over the reactor based ^{185}Re(n,γ)^{186}Re process is the carrier free quality. Reaction with deuteron appeared to produce higher purity of ^{186}Re (> 99%).[55] The alternative ^{188}Re, by the way, can be also produced with cyclotrons. In the Shanghai Institute of Nuclear Research Academia Sinica, a 30 MeV proton cyclotron was imported from IBA (Belgium) in 1997 to produce among others ^{89}Sr, ^{188}W and ^{188}Re.[56] Tungsten-188 also serves as the parent isotope for the production of ^{188}Re, like ^{99}Mo is for the production of ^{99m}Tc.

Iridium-191 (^{192}Ir)

^{192}Ir, used in high-dose rate brachytherapy, can be also made with cyclotrons. In 2005 researchers produced ^{192}Ir according to the reaction ^{192}Os(p,n)^{192}Ir. They concluded: "In terms of yield and purity of ^{192}Ir the reactor method appears to be superior; the only advantage of the cyclotron method could be the higher specific activity of the product." Two years later other researchers made ^{192}Ir according to the reaction ^{192}Os(d,2n)^{192}Ir with a substantial better yield and purity.[57]

Lutetium-177 (^{177}Lu)

As noticed in Chapter 4 ^{177}Lu is projected to become as important as iodine-131 (^{131}I), the second most used medical radioisotope. Several countries have already begun or are planning medium to large scale production of this radioisotope. Currently this β-emitter is mainly produced in a nuclear reactor in a mixed form of two different states: ^{177m}Lu and ^{127g}Lu. The first one is a long-lived radionuclidic impurity and the second one is used in radiotherapy. Deuteron irradiation on very highly enriched ^{176}Lu target or deuteron induced reactions on ^{176}Yb in a cyclotron is leading to a significant amounts of a very high radionuclidic purity ^{177g}Lu, not contaminated by the long-lived metastable level ^{177m}Lu.[58]

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[52] Petrusenko, Yu.T. et al.; Analysis Of Data Arrays On Cyclotron Production Of Medical Radioisotopes. Problems OF Atomic Science Aan Technology, 2009. Series: Nuclear Physics Investigations (51), p.82-88. http://vant.kipt.kharkov.ua/ARTICLE/VANT_2009_3/article_2009_3_82.pdf
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[53] Spahn, I.et al.; New nuclear data for production of ^{73}As, ^{88}Y and ^{153}Sm: important radionuclides for environmental and medical applications. International Conference on Nuclear Data for Science and Technology 2007. nd2007.edpsciences.org/articles/ndata/pdf/2007/01/ndata07351.pdf

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[56] Lin, Yuzheng (Tsinghua University, Beijing, China); Applications of Low Energy Accelerators in China. Proceedings of the Second Asian Particle Accelerator Conference, Beijing, 2001 cern.ch/AccelConf/a01/PDF/FRAM01.pdf

[57] Tárkányia, F. et al.; Study of the 192Os(d,2n) reaction for production of the therapeutic radionuclide 192Ir in no-carrier added form. Applied Radiation and Isotopes Volume 65, Issue 11, November 2007, Pages 1215-1220.
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[58] Bonardi, M.L.; Deuteron cyclotron production of high specific activity NCA Lu-117g for metabolic radiotherapy, as a competitive method to neutron activation in nuclear reactor. (paper) NRC7 - Seventh International Conference On Nuclear And Radiochemistry. Budapest, Hungary 24-29 August 2008 http://www.nrc7.mke.org.hu/pdf/presentations/abstract249.pdf
Hermanne, A. et al.; Deuteron-induced reactions on Yb: Measured cross sections and rationale for production pathways of carrier-free, medically relevant radionuclides. Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms Volume 247, Issue 2, June 2006, pp. 223-231.

4.2 Cyclotron-produced isotopes as an alternative for reactor-produced isotopes

Bismuth-213 (^{213}Bi)

^{213}Bi is not a necessary medical isotope. For example a recent study shows that thorium-226 (^{226}Th), a cyclotron produced radionuclide, has a higher efficiency in overcoming chemo- and radioresistance in myeloid leukemia cells compared to ^{213}Bi.[59]

Chromium-51 (^{51}Cr)

^{51}Cr is also not a necessary medical isotope. Many publications in the 1970s and 1980s show that indium-111 (^{111}In), a cyclotron-produced isotope, is a better labeling agent for blood cells than ^{51}Cr.[60] More recent studies confirm that ^{111}In is superior as a radiolabel for platelet scintigraphy when compared with ^{51}Cr or ^{99m}Tc.[61]

Xenon-133 (^{133}Xe)

^{133}Xe is one of the fission products of a research reactor. Until the 1990s ^{127}Xe was the preferred alternative. Except by the reactor, this isotope is produced solely by high-energy accelerators, such as the Brookhaven Linac Isotope Producer, which do not operate year round. This circumstance contributed to the decision by Mallinckrodt Medical Inc. (Covidien), the only commercial supplier in the United States, to withdraw the isotope from the market. Nowadays, ^{127}Xe is made by a reactor. However, it isn't necessary if a number of linacs are operating for the continue supply of these rarely used medical isotopes.[62]

4.3 ADS alternatives for reactor-produced isotopes

Yttrium-90 (^{90}Y)

According to 2007 IAEA data "there is a large demand for yttrium-90 for radionuclide therapy and consequently there is increasing interest in the isolation and purification of the parent radionuclide ^{90}Sr from spent fuel."[63] There is, however, an alternative method to the fission product based on the ^{90}Sr/^{90}Y generator. By activating zirconium-90 (^{90}Zr) with neutrons, generated through (p,xn) reactions during 33 MeV proton irradiation of natural tungsten or other targets, ^{90}Y can be produced according to the ^{90}Zr(n,p)^{90}Y reaction or the ^{93}Nb(n,α)^{90}Y reaction. These methods can produce two states of ^{90}Y: ^{90g}Y and ^{90m}Y in significant amounts. ^{90g}Y radiopharmaceuticals have been used together with ^{111}In radiopharmaceuticals for cancer therapy and ^{90m}Y for imaging (diagnosis). ^{90}Y radiopharmaceuticals containing ^{90m}Y could solve long-standing problems associated with the use of reactor-produced ^{90g}Y together with ^{111}In for imaging.[64]

4.4 Other alternatives for reactor-produced isotopes

Cobalt-60 (^{60}Co)

^{60}Co sources provide relatively high energy gamma rays for radiotherapy which are suited for treatment of head and neck cancers and tumors like breast cancers and soft tissue sarcomas of extremities. However, they are not adequate for the treatment of other tumors and another disadvantage is that they have to be replaced within 5-7 years. Disposal of decayed source is another major concern. High energy Linacs for external radiation therapy are expensive, a 6 MV Linac, however, compares favorably in terms of costs with a Cobalt ^{60}Co unit.[65]

Lutetium-177 (^{117}Lu)

^{117}Lu is a rather recently introduced isotope, currently mainly produced by a nuclear reactor. The energy emitted by ^{177}Lu, however, is comparable with the energy emitted by the cyclotron-produced scandium-47 (^{47}Sc). Before and during the introduction of ^{177}Lu pharmaceuticals experts noted that similar results could be made with ^{47}Sc. This example is illustrative for many reactor-produced isotopes. One can always find analogue cyclotron-produced isotopes, provided that there is the willingness to invest in the production of these isotopes and their medical applications.[66]

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Grignon, C.; Nuclear medical imaging using β+γ coincidences from ^{44}Sc radio-nuclide with liquid xenon as

4.5 Advantages of the cyclotron

According to a 2007 survey of the International Atomic Energy Agency it is estimated that there are about 350 cyclotrons available with many dedicated to the production of positron emission tomography (PET) isotopes.[67] In 2009, the IAEA stated: "The production capacity of radioisotopes using cyclotrons has increased. [..] In response to growing demand for fluorodeoxyglucose (FDG), tabletop cyclotrons (~7.5 MeV), [..] are under development
and are expected to be adopted by major hospitals worldwide.[68]

The contrast between a nuclear reactor and a cyclotron is startling. Reactors are huge complex machines in running 24 hours a day, surrounded by layer upon layer of security and shutdown systems, and with radioactive waste that will last for millennia. The typical medical cyclotron is varying from tabletop format to a big metal box in a room that measures about 8 by 10 meters.

Cyclotrons have a number of advantages over nuclear reactors for radioisotope production, such as safety, cheaper operating and decommissioning costs. Because cyclotrons are powered by electricity rather than the uranium fission reaction of a nuclear reactor, they generate far less than 10% of the waste of research reactors. In addition, cyclotron-produced radwaste is far less hazardous than radwaste produced by a research reactor. All cyclotron produced radwaste, including contaminated decommissioning parts, is treated as low level radioactive waste and stored in an authorized storage area.[69] In the US this waste is classified as *naturally occurring and accelerator produced radioactive material* (NARM).[70] Finally, cyclotrons pose no risk in relation to nuclear weapons proliferation since they do not use high-enriched uranium (HEU) targets, as used in research reactors, and there is no need for controlled chain reactions producing bomb-grade nuclear material.

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Chapter 5

RECENT DEVELOPMENTS AND PROSPECTS IN RADIOISOTOPES PRODUCTION

Last year a commission of experts has advised the government of Canada, one of the major medical isotopes producing nations, to invest in accelerators for the production of among others radioisotopes, currently made by research reactors.[71] Though the expert panel kept the option open to build a new research reactor, the Canadian government decided to cancel this option based on good arguments: *"From a purely isotope perspective, outside the considerations of the other missions of a research reactor, the Government finds that the very high costs and very long lead times make this a less attractive option than others. Based on the experience of other countries, it would likely take a decade or more to bring a new research reactor on stream. Also, the significant fixed costs and production capacity would be disproportionate to Canada's isotope needs and could not be recouped from the market. Waste liabilities associated with long-term reactor-based isotope production would be significant and again difficult to fully recover."* [..] *"A research reactor is only one piece of the linear supply chain that exists today. Replacing one piece of a linear supply chain, such as simply replacing the NRU with another reactor, would do little to develop the diversity and redundancy that the Panel believed were critical for ensuring security of supply. The lesson learned is that more should be done to create cross-linked and distributed supply chains that are not as vulnerable to single-point failures. An announcement that a new research reactor would be built in Canada to produce medical isotopes would discourage investment in alternative sources of supply, both in Canada and in other countries. The supply chain would continue to remain vulnerable to the single-point-of-failure problem that exists today, and generators would likely be manufactured outside of Canada."*[72]

Such a decision had to come to this in the end. The long history of choosing primarily research reactors for isotopes production has miserably failed. The continued disruptions in the supply of

radiopharmaceuticals are the result of making wrong decisions. The development of the Maple-reactors in Canada is a perfect example to show the far-reaching consequences of such policy.

5.1 The MAPLE failure

In the mid 1990s the Canadian producer of radioisotopes MDS Nordion commissioned Atomic Energy of Canada Limited (AECL) to build two nuclear reactors. The two research reactors were named to the project name under which they were built: *Multipurpose Applied Physics Lattice Experiment* (MAPLE). Both reactors, Maple 1 and Maple 2, were especially designed for the production of molybdenum-99 (^{99}Mo). Each of these reactors was to have the capacity to meet the world's ^{99}Mo needs, so that each would serve as a backup for the other. With the prospect of the Maple reactors entering service in early 2000, the development of alternative production methods for ^{99}Mo or ^{99m}Tc never reached maturity. And meanwhile, after more than ten lost years for the development of cyclotron-produced isotopes, AECL cancelled the Maple Project in May 2008. The Canadian Nuclear Safety Commission (CNSC) denied a license to operate the Maple reactors due to a design fault. In 1996, MDS Nordion agreed with AECL to pay US$140 million for the design, development and the construction of the two new reactors. In 2005, five years after the reactors had to be delivered, these costs were more than doubled (US$330 million) without the prospect that they will entering in service. Canadian radio-isotopes are therefore still produced with the aged National Research Universal (NRU) reactor of which the current license expires in October 2011.[73] Meanwhile the construction the new research reactor in the Netherlands will start within a few months.

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[71] Report of the Canadian Expert Review Panel on Medical Isotope Production, 30 November 2009. http://nrcan.gc.ca/eneene/sources/uranuc/pdf/panrep-rapexp-eng.pdf
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[72] Government of Canada Response to the Report of the Expert Review Panel on Medical Isotope Production. March 31, 2010
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The total costs are projected on €500 million and the reactor has to be operable from 2018.[74]

5.2 Medical isotopes production is currently depending on five rickety reactors

Currently, around 95% of the worldwide medical reactor-produced isotopes are made with five aged research reactors in Belgium, Canada, France, The Netherlands and South-Africa which are frequently shut down for a longer period of time. The Canadian NRU reactor and the Dutch HFR together supply for about 80% in the worldwide demand of ^{99}Mo, of which 60% is delivered by MDS Nordion (Canada) and the remaining part by Covidien Mallinckrodt (The Netherlands). The other three reactors supply Europe and parts of Asia and also serve as back-ups when one of the large producers break down because of maintenance. All these reactors are 43 to 52 years old (mid 2010). The life span extension of the reactors cause - and will inevitably remain to cause – problems due to age. The problems are not associated with the reactors themselves but with the infrastructure: leaking containment vessels and leaking pipes buried deep in shielding walls. Such problems are difficult to isolate and solve, resulting in prolonged shutdowns. The smaller reactors could increase their production capacity, such as the much named *Maria* research reactor in Poland (more than 35 years old), but none of these reactors has the capacity of the HFR or the NRU to take over the production rate of radioisotopes. The announcement of France to postpone major repairs to the OSIRIS planned in 2010, because of the shutdowns of the NRU [May 2009 until August 2010(?)] and the HFR [February 2010 until August 2010(?)] will not bring any relieve in the continuing severe medical isotope shortages. Radioisotopes production with these wobbly nuclear reactors has been appeared very uncertain in the past years.[75]

Main Isotope Production Facilities (IAEA May 2010)

Country	Name	Reactor Type	Criticality Date
Belgium	BR-2	Tank	1961-06-29
Canada	NRU	Heavy Water	1957-11-03
France	OSIRIS	Pool	1966-09-08
Netherlands	HFR	Tank in pool	1961-11-09
Poland	MARIA	Pool	1974-12-18
South Africa	SAFARI-1	Tank in pool	1965-03-18

5.3 Can Pallas overcome the acute shortage of medical radioisotopes?

The current High Flux Reactor in Petten, The Netherlands, will be replaced by the *Pallas*. This new research reactor has to enter service in 2018. This means under the most favorable conditions, because there are normally years of delays in the construction of nuclear reactors. Considering the highly uncertain production of the NRU (permanently shut-down in 2011) and the HFR, Pallas offers no solution for a safe and secure supply of technetium-99m in the short term. Also the French Osiris reactor will shut down for a longer period by the end of 2010 or in 2011, the permanent shut-down is in 2015. Possibly Australian and German research reactors can take over a part of the production, however, as said before this will never be sufficient to keep up the supply of medical isotopes.

The recent decision of the Canadian government to cancel the construction of a new research reactor and to invest in the production of cyclotron-based radioisotopes have to be seen against this background. Hopefully this will be the first step in the revival of the original radioisotopes production methods: the charged particle accelerators. The development of a proton-induced neutron accelerator or the accelerator driven system (ADS), a sub-critical assembly driven by an accelerator, shows promising results. Such systems can be used until alternative medical isotopes produced by accelerators will arrive on the market. AMIC, a US company, in conjunction with researchers from a number of U.S. universities has tested ADS successfully for the production of molybdenum-99 and expects to start production in the nearby future to cover the US demand for technetium.[76] ADS is also a good alternative for the production of yttrium-90 (^{90}Y), holmium-166 (^{166}Ho), erbium-169 (^{169}Er), and iodine-125 (^{125}I), projected to be produced by Pallas.

[74] Bouw Pallas kernreactor vertraagd http://www.rtvnh.nl/nieuws/index.asp?newsid=106000

[75] Ruth, Thomas J.; The Medical Isotope Shortage: http://www.aps.org/units/fps/newsletters/200910/ruth.cfm

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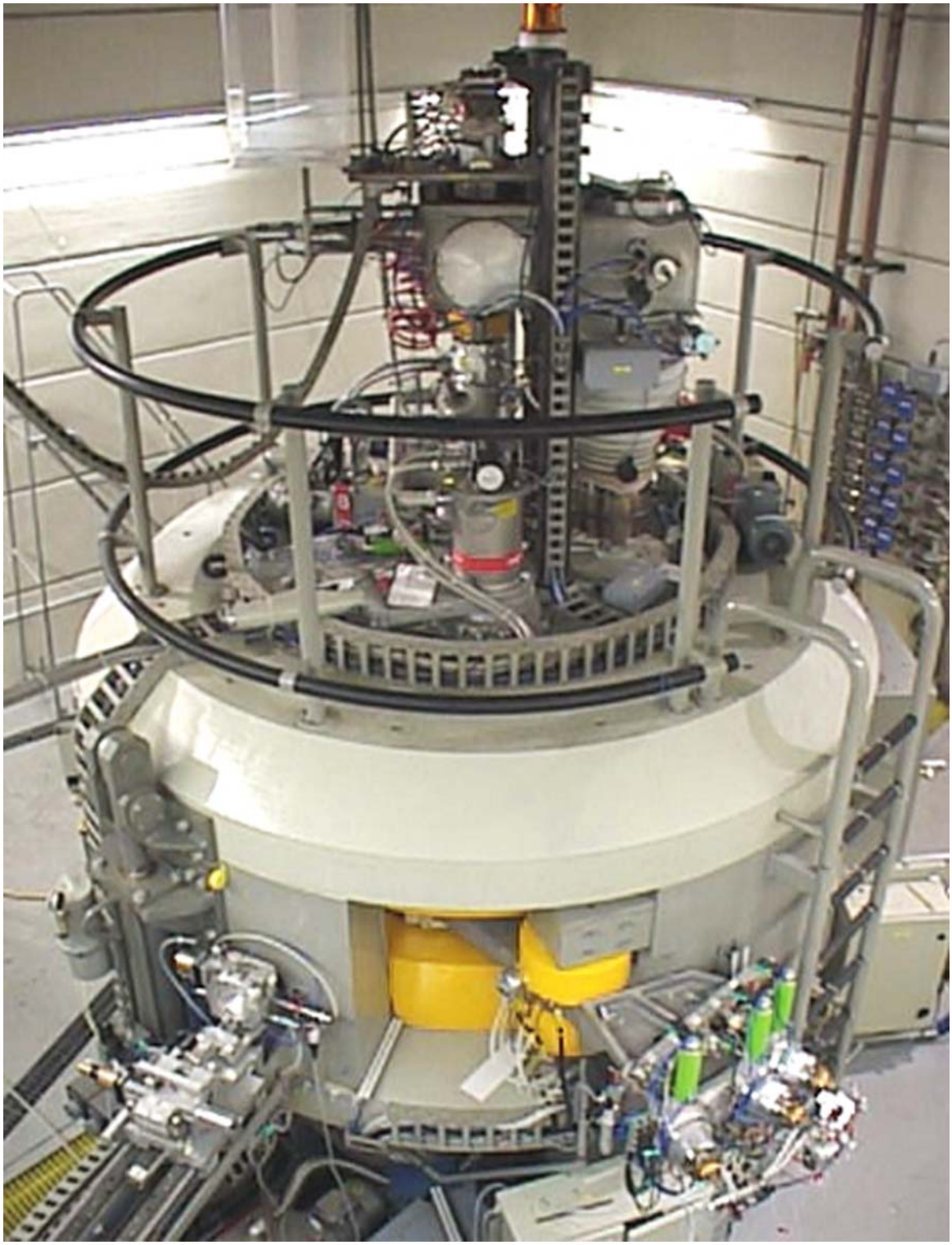

Chapter 6

DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

Until 2007 there was an almost uninterrupted supply of cheap subsidized reactor-produced isotopes, there was no need to search for alternatives. From January 2007 until February 2010 there has been at least six periods of serious disruption to supplies and since February 2010 after the shut-down of the HFR in Petten the world experiences the most serious period of medical isotopes shortages. Only in Canada the first disruptions were followed by serious debates on how to secure the domestic supply of radiopharmaceuticals in the nearby future and the future.

6.1 Discussion

The development of accelerator-based production of medical isotopes has always been thwarted in favor of the production with nuclear reactors. Policy-makers are opting for research reactors, because they offer large scale production of medical isotopes. The continued disruptions, however, have proven that the reactor method is not safe and secure. And why should the isotopes production be dependent on a few worldwide monopolists? Cyclotrons offer the possibility to produce hospital-based medical isotopes.

Clinical and biomedical research communities in Canada have begun to look for alternative ways to produce technetium-99m needed for vital clinical procedures and also to explore the potential of alternative medical isotopes to replace technetium as the radiopharmaceutical label in clinical practice. Developments in this field can be observed in newspaper articles.
Let's take for example a cardiac treatment center. Traditionally, technetium-99m covers about 80% of the isotopes supply used in this discipline. Due to the severe disruptions in the supply of technetium, cardiologists and other medical specialists are searching for the supply of cyclotron-produced isotopes that can be used as an alternative. These include cyclotron-produced technetium or PET isotopes that are performing better than technetium-based modalities. Cardiac PET includes a cyclotron where the lab makes its own medical isotopes. There is no longer any fear for shut downs in the supply of isotopes. PET rubidium-82, generated from cyclotron-produced strontium-82, is a major alternative to technetium. ^{18}FDG-PET imaging tackles large arteries with atherosclerosis. The demand for cyclotron-produced thallium (heart) and iodine (thyroid) is increasing at the expense of reactor-based technetium used in cardiology.[77] The same trends can be observed in other medical disciplines among which cancer imaging and therapy. Also in the Netherlands medical centers have been started to look at other sources to secure their isotopes supply as a consequence of the ongoing crisis. More and more medical disciplines switch over to cyclotrons. Recently such decisions were made in Dutch hospitals in Alkmaar and Den Bosch.

Today Canada is frontrunner in the development of isotopes production by accelerators.
The Canadian subatomic physics laboratory TRIUMF (TRI University Meson Facility) is involved in projects for accelerator-based production of technetium-isotopes and the production of gallium compounds for use as radiopharmaceuticals as alternatives to existing technetium-radiopharmaceuticals. The molybdenum-99 manufacturing method of TRIUMF involves the use of a highly intense photon beam. Instead of thermal neutrons as in the reactor, electrons are used to irradiate the target material. Instead of high-enriched uranium targets as in reactors (vulnerable for nuclear proliferation), natural uranium is used as target material. In addition, the production of the positron emitter technetium-94 is proposed. This means that the produced technetium-isotopes can make use of the existing technetium-based radiopharmaceuticals for PET as well as SPECT imaging. The second project is the production of gallium-68 (^{68}Ga) and gallium-67 (^{67}Ga) as alternatives to the ^{99m}Tc radiopharmaceuticals. A benefit of this alternative is that ^{67}Ga will allow users the option of imaging using SPECT while ^{68}Ga is a generator produced PET isotope that enables access to these agents in facilities without cyclotrons. This project is in co-operation with the Canadian partner MDS-Nordion, a leading global provider of medical isotopes and radiopharmaceuticals in molecular medicine.[78]

[77] Canwest News Service 11 July 2009: The new face of nuclear medicine: Radioactive dyes made at an Ottawa heart institute are saving patients from invasive procedures.
http://www.vancouversun.com/health/face+nuclear+medicine/1781407/story.html

[78] TRIUMF Submits Plans for Medical Isotope Alternatives. 17 Sep 2009
http://www.triumf.ca/headlines/current-events/triumf-submits-plans-for-medical-isotope-alternatives

Meanwhile, another Canadian company - Advanced Cyclotron Systems, Inc. (ACSI) - a world leader in the design and manufacturing of cyclotron equipment, submitted a proposal for a *National Cyclotron Network to Produce Medical Isotopes* that would fulfill all the Canadian 99mTc needs. ACSI's TR24 cyclotron, the only 24 MeV cyclotron of its kind in the world, can produce PET and SPECT isotopes including ^{99m}Tc, ^{123}I and ^{68}Ge. ACSI is proposing the direct production of ^{99m}Tc on TR-24 cyclotrons as suggested by the Canadian Expert Review Panel on Medical Isotope Production. "A national network of eight strategically placed cyclotrons provides both a scalable and reliable source of isotopes and is financially self-supporting following a modest initial capital investment. Leveraging existing cyclotron technology and distribution centers, the network can begin operations within eighteen months (from January 2009) and would meet the entire Canadian medical isotope needs in two to three years." According to their estimations the Canadian demand for ^{99m}Tc could be covered by cyclotron production between 2012 and 2014, much earlier as foreseen in the projected time schedule of the expert panel.[79]

The preparations for the construction of the Pallas reactor are in full swing. Though officially there hasn't been made a decision yet about the location (Zeeland or Noord-Holland), the board of the Dutch province Noord-Holland has invested €40 million in the construction of the Pallas. For a fraction of this amount Canadian researchers are working on solutions to tackle the urgent problems in the domestic supply of medical isotopes in the nearby future. It is highly likely that Canada will cover its domestic demand for technetium by accelerators in 2014.

The prices of Canadian built medical cyclotrons are varying from €1,75 million to €4,20 million. Depending on the isotopes production, they can be delivered within a few months or a few year. The construction costs for the Pallas are estimated on €500 million.

6.2 Conclusions

As described in Chapter 5 seven of the eight most popular reactor-based medical isotopes: molybdenum-99 (^{99}Mo) (or direct production of ^{99m}Tc), iodine-131 (^{131}I), phosphorus-32 (^{32}P), , strontium-89 (^{89}Sr), samarium-153 (^{153}Sm), rhenium-186 (^{186}Re) and lutetium-177 (^{177}Lu) can be easily made in substantial amounts with particle accelerators. The remaining popular reactor-based isotope chromium-51 (^{51}Cr) is not an essential isotope. Similar cyclotron-produced isotopes performs better. Therefore, the widely used slogans of the nuclear industries indicating that reactor-based medical isotopes have been essential for nuclear medicine are false. The question "Is it possible to ban the use of a nuclear reactor for the production of radiopharmaceuticals?" can be answered with a straightforward 'yes'.

This means that Pallas is not needed for the production of medical isotopes and leads one to suspect that other interests are involved. In the first place these are the commercial interests of Covidien – one of the subsidized monopolists on the global market of reactor-based medical isotopes, and in the second place Nuclear Research Group (NRG), which very much likes to play a major role in the area of nuclear consultancy and nuclear research. In addition it is important for the image of nuclear energy to maintain the coupling with the production of medical isotopes in the public debate and in the public perception.

A decision to develop radiopharmaceuticals with the use of reactors or cyclotrons is simply a choice and not a story of *and* reactors *and* accelerators. Cyclotrons are a logical choice. It saves costs and the environment. Moreover, cyclotrons guarantee a safe and secure supply of medical isotopes. Disruptions in the supply of isotopes will be over forever.

6.3 Recommendations

The Canadian researchers who invented the idea of a National Cyclotron Network to Produce Medical Isotopes show the route to a safe and secure production of radioisotopes. It can serve as a model for other nations. It also shows how quickly the transformation of a reactor-based to an accelerator-based production of medical isotopes can take place. If the Dutch government should choose now for such a transformation, like the Canadian government does, the cyclotron-based isotopes could easily cover the Dutch domestic demand for medical isotopes in 2016. Four cyclotrons in Groningen, Utrecht, Rotterdam and Eindhoven are enough to cover the Dutch domestic demand for technetium.

The use of PET/CT with PET isotopes in imaging and therapy presents a better alternative than gamma camera scintigraphy and SPECT with mainly reactor-produced isotopes. The share of reactor-produced medical isotopes will definitely shrink in the coming decades, while the share of PET isotopes is increasing steadily. Policy-makers can anticipate on this trend by making a choice for cyclotron-produced medical isotopes. Besides PET isotopes, this report has shown that all relevant reactor-based isotopes can

[79] ACSI Announces New TR-24 Technetium Cyclotron, 10 January 2009 http://www.advancedcyclotron.com/news/acsi-announces-new-tr-24-technetium-cyclotron

be made by an accelerator. In addition, investing in cyclotrons also means investing in research for the development of new cyclotron-based pharmaceuticals, just like the current highly popular PET-pharmaceuticals.

Source: The entire report "*Medical radioisotope production without a nuclear reactor*" (38 pages) is available at: www.laka.org/medical-isotopes.html

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