INTERVIEW: DR. GUY TURQUET DE BEAUREGARD

We Need to Expand Medical Isotope Production!

Dr. Turquet de Beauregard, a nuclear physicist with 15 years experience in nuclear medicine, is the vice president of AIPES, the Association of Imaging Producers & Equipment Suppliers, based in Brussels. AIPES serves the different regulators as a coordinating body for all disciplines in nuclear medicine, from radiopharmaceutical companies to camera suppliers. It also conducts public education, providing an overview of the current crisis of medical isotope shortages.

Dr. Turquet de Beauregard spoke with 21st Century *correspondent Vyron Lymberopoulos on Feb. 1, about the shortages that have delayed medical diagnoses and treatments for hundreds of thousands of patients worldwide.*

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Question: There are a limited number of reactors and processing facilities worldwide. Why is that? Why are we so far behind in the use of medical isotopes?

Nuclear medicine emerged as a result of many programs of the Manhattan Project during the Second World War. Many reactors were built by government agencies at great expense. At that time there was little concern for industrial or medical applications; most were built for power generation.

Nuclear medicine began as a small partner of these power reactors, taking just a small percentage of the time of the reactor. Not one single reactor was designed dedicated to nuclear medicine. The industry piggybacked along nuclear power, which made things easy.

There are basically three methods to produce a medical isotope:

(1) ***Cyclotrons.*** These are a kind of particle accelerator, and you need many of them.

(2) ***Irradiation for activation*** in a power reactor, which can be done in many reactors.

(3) ***The fission process.*** This is most important method today, extremely productive. Fission of uranium creates the by-products of molybdenum-99 and other isotopes. It is a very

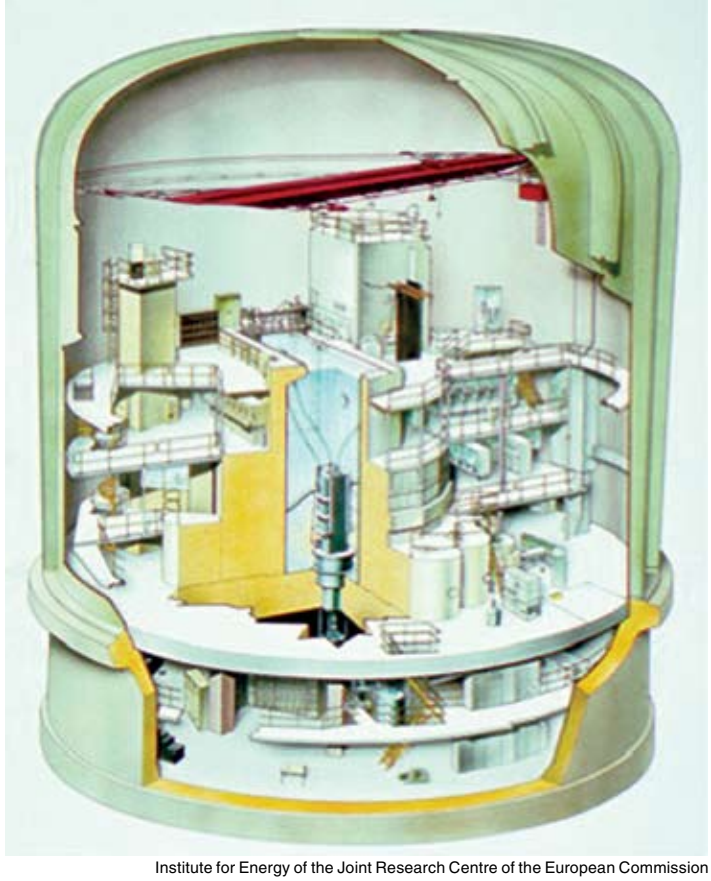
Medical Isotope Sources and Use

At present, six reactors provide more than 95 percent of the molybdenum-99/technetium-99m supply worldwide. These are: NRU (Canada), HFR (the Netherlands), BR2 (Belgium), OSIRIS (France), SAFARI (South Africa), and OPAL (Australia). The remaining 5 percent is produced by CNEA (Argentina), BATAN (Indonesia), and KARPOV Institute (Russia).

Eighty percent of all nuclear medicine procedures worldwide are used for diagnosing disease. This includes:

Heart pathology	12 million procedures
Bone pathology	10 million
Lung pathology	5 million
Thyroid pathology	5 million

Source: AIPES



Institute for Energy of the Joint Research Centre of the European Commission

The High Flux Reactor at Petten, now shut down for maintenance, supplies 70 percent of Europe's molybdenum-99. The HFR is a 45-megawatt tank-in-pool-type reactor which is cooled and moderated by light water. It has 20 in-core and 12 poolside irradiation positions, in addition to 12 horizontal beam tubes.

Institute for Energy of the Joint Research Centre of the European Commission

Looking down the core of the Petten reactor. The High Flux Reactor also conducts research on fission fuel and materials. The HFR has used low-enriched uranium fuel since 2006.

complex process. Few reactors in the world have the license to do it, and most of them were built in the 1960s. They are now near the end of their lifetime, and there are safety issues, and security issues of proliferation involved.

Only recently have reactors been built that are dedicated to the production of medical isotopes. Canada was very active in the medical isotope production, and 15 years ago they planned to address the medical isotope shortage by building two reactors dedicated to nuclear medicine. Both these Maple reactors failed, because of design problems. There are many lessons to be learned from this.

Question: What is the difference between Europe and the United States in medical isotope production?

Everything for North America is based in Canada. The equivalent of AIPES in the United States is called CORAR, the Council on Radionuclides and Radiopharmaceuticals.

Question: When the High Flux Reactor (HFR) in Petten, the Netherlands, is closed for maintenance, what impact will this have on worldwide supply?

In Europe, we will lose 70 percent of molybdenum-99 production; worldwide we will lose 30 percent. So not having the HFR will cause major problems. Nuclear medicine doctors will be obliged to switch to other isotopes, like thallium for SPECT (single photon emission computer tomography scans), which is produced by cyclotrons.

Doctors will have to make good use of the isotopes that are delivered to hospitals. They will have to be extremely conservative in their use of technetium-99m solutions, and be much more efficient than before.

There will be an even bigger problem when both the HFR and the Canadian Chalk River facility are closed at the same time. In order to assure a minimum availability of medical isotopes, AIPES tries to organize coordination between the reactors in the Netherlands, Belgium, France, and South Africa. Some urgent procedures can use alternative isotopes, but many procedures will have to be delayed by a couple of weeks.

As for alternatives, the problem is that imaging with nuclear medicine in some specific cases is far superior to the results of MRI and X-ray imaging.

Question: What are the bottlenecks in regulating medical isotopes?

Nuclear medicine is a very regulated world both on the national and international level. Regulation in the nuclear world is separated into the manufacturing of isotopes, which is highly regulated, and transport, which is also highly regulated. There are also security regulations as a result of the threat of terrorism after 9/11.

Question: What must we do to expand the production of medical isotopes?

We need, as a capacity, two and a half times the current consumption in Europe to secure steady molybdenum-99 availability because of nuclear cycles and reactor maintenance. Now we are far below that. We must organize the world to do this, and there are ways to do it. This is a top priority, to expand production of medical isotopes.

Several solutions exist. First, present-day research reactors could be used for medical isotope production using fission. In addition, in the future, we could use the reactors that are now under construction. We can turn the crisis into an opportunity.

Second, we can expand the use of cyclotrons to produce isotopes, that is, positron emitters like fluorine-18 and gamma emitters like thallium-201. The production of isotopes with cyclotrons for PET (positron emission tomography) applications is a way to expand production. The drawback is that cyclotron isotope production is very expensive compared to fission in a reactor, but clearly it is a solution for the future.

Also, for the emerging nations, this technology is easier to transfer. The cyclotron isotopes have a short half-life measured in hours. So they have to be produced close to where the camera and the patient are located.

Now, note that the progress in nuclear medicine is as fast as the microprocessor industry. Thanks to camera efficiency and

ATOMKI

The MGC-20E cyclotron of of Hungary's ATOMKI. Particle accelerators like this one are used to produce the radioisotopes for PET and SPECT imaging.

the increased speed in calculations, where we once needed two hours to treat one patient, we now need only 10 minutes for one patient, thanks to the new cameras using the same isotopes!

Question: Can molybdenum-99 be produced without using uranium-235?

The answer is yes, you can activate molybdenum-98 by the irradiation method, but the efficiency is extremely poor, compared to the fission method.

Molybdenum-98 is a stable isotope found in nature. When you irradiate it in a reactor, it gains a neutron and becomes molybdenum-99. The problem is, the costs of this process are high, and it is not yet approved by the regulating agencies.

Question: Recently, a small research reactor at Delft University in the Netherlands has offered to take over part of the production of molybdenum when the HFR shuts down for maintenance.... Can a research reactor, which is used to train nuclear engineers, be used to produce molybdenum-99?

Let me talk about how the reactor must be designed for this process. To use it for isotope production, you place a target near the reactor core and "cook" it for a week. Then the target is sent to a processing facility to extract the molybdenum-99.

There are different regulatory issues that come up, when you add fission into the core or near the core. You must show that there is no critical safety issue hiding with this fission product near the core. From a nuclear physics safety point of view, you must produce a safety dossier for the authorities, and you must show that you can extract the target and store it safely in containers. If the design of the reactor is already set up for this, that is good. But if it isn't—take for example in Munich: It took three years to build the required mechanism to transfer targets from the core to the containers to be shipped to the processing facilities. You need a safety dossier to check all the different steps.

I'm just mentioning what is needed in general, because I don't know this particular Delft reactor.

Question: How long would it take to license a reactor to start producing medical isotopes?

I don't know, because I'm not the authority. But as industry spokesmen, we welcome any good initiative that is appropriate for safe production.

Question: What are the bottlenecks in transporting medical isotopes?

First you need a license for transportation. It's a just-in-time product, and has to move quickly. For road transport of nuclear products there are certain regulations but no major bottlenecks. Air transportation is different because of security issues. People don't want to keep things in a plane, which they think (erroneously) could be used as a bomb. People working with radioactive parcels need a security clearance. The process needs to be carefully monitored from manufacturing, processing, and shipping, until delivery at the medical facility for use. A major bottleneck is the security clearance of the operatives handling the isotopes at any stage of the process. A second bottleneck is the denial of shipment by captains or drivers who do not wish

LeRoy N. Sanchez/LANL

A technician using hot-cell remote manipulators in the Isotope Production Facility at the Los Alamos Neutron Science Center.

to carry radioactive material.

Most of the time this is a communication issue, and we have to work on this. People easily mistake medical isotopes for "nuclear waste," which has an extremely long half-life. The medical isotopes shipped all have short half-lives. They are injected in patients for medical procedures, for diagnosis of disease and to cure people or save or prolong life.

Question: Would nuclear medicine benefit from the lifting of a transport ban on medical isotopes by certain transport companies?

Definitely yes, especially if companies located close to an isotope-producing facility would resume the transport of medical isotopes; that would be very good news. If they could look at the problem and see it is not as dangerous as they thought, that would be a very positive thing to show to the world. It could be dangerous, but it is so regulated, monitored, and controlled, that people should be much more confident with these products. There have been extremely few incidents. We have to report any problem, even the smallest problem, and there are very few.

So, communication could be improved to inform the people involved what they are transporting—and what it is not! Also by pointing out the beneficial side of nuclear medicine to the general health of the population around the world.

Question: What is the situation in the emerging nations?

Outside Europe there is good information from a limited number of countries, primarily North America and Japan. I have no information on China or India; the government there is working with local manufacturers—it's purely a local market. Russia has many reactors and very good knowledge of nuclear physics. AIPES is focussed on Europe, so probably the IAEA is better equipped to answer this question.

Question: How do you rate the prospect of future isotope production by means of thermonuclear fusion?

Well, I'm surprised by this question; I haven't a single idea

The Moly/Technetium Cow

The most efficient way to create molybdenum-99 is by the fissioning of the fissile isotope of uranium, U-235. When uranium nuclei fission, several fission products are created, and about 6 percent of them are molybdenum-99.

To produce Mo-99 in a reactor, uranium targets are placed on flat plates and inserted into target holders on a rack, which is positioned at the outer lining of the reactor vessel. For one week, the neutrons from the reactor core bombard the targets, splitting the uranium nuclei. This is called "cooking" the target.

The targets are then removed from the core, placed in containers, and transported to the processing facility. There, technicians working remotely in hot cells (see photo, p. 48) chemically separate the molybdenum from the uranium targets. The molybdenum is first produced as a salt, sodium molybdate, which is then diluted in water. Then it is stored in a stainless steel flask (the cow).

Molybdenum-99 has a half-life of 66 hours, and decays to produce technetium-99m, a gamma emitter (140 keV) which has a half-life of only 6 hours. Each batch of molybdenum fills more than 500 cows, and each cow can serve between 100 and 200 patients. Quick transport is required, because the moly cow loses 22 percent of its product every 24 hours.

To milk the moly cow, the technetium-99m is washed from the molybdenum/technetium solution by an aqueous solution. The technetium is then coupled to a specific carrier, a protein, for administering it to a patient.

—Vyron Lymberopoulos

MDS Nordion

A shipping box for canisters of Mo-99.

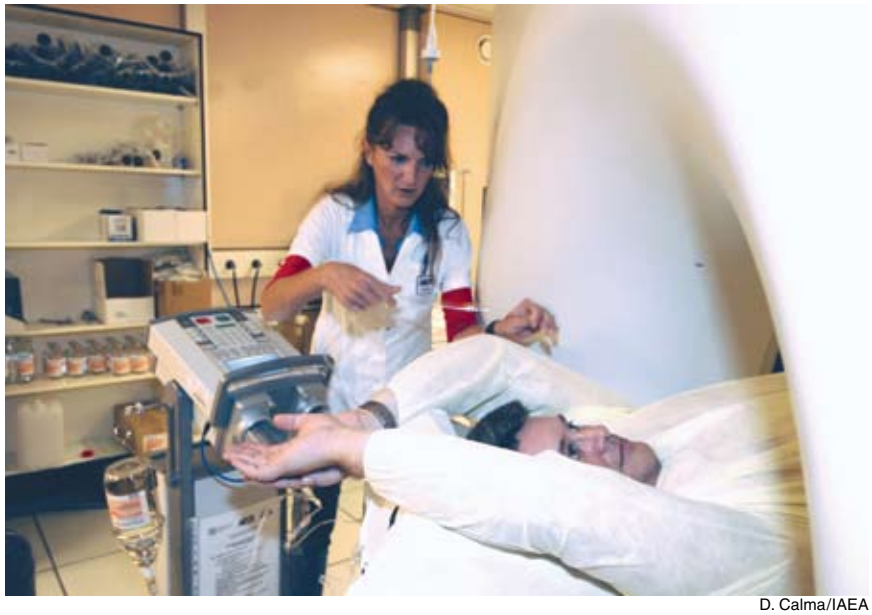
MDS Nordion

A moly "cow," which is milked to supply the short-lived isotope technetium-99m for medical diagnostic procedures.

on that. I'm a nuclear physicist and know very well what nuclear fusion is. I was at the Los Alamos and Lawrence Livermore labs, but I'm not up to date on the latest progress. Maybe my great-great-grandchildren will see it? Right now, we don't know how to create continued fusion reaction. The ITER project in France is a worldwide project to build a fusion reactor. The fusion reaction produces high-energy neutrons, which would have to be slowed down. But to be honest, I have no idea of any prospect of isotope production by means of fusion.... If you can manage fusion, many questions are answered.

Question: What is the most important isotope produced today to save lives of people?

Clearly it is molybdenum and technetium; next to that is fluorine-18, which is produced in cyclotrons for PET. Worldwide, approximately 40 million molybdenum/technetium procedures are performed each year, and about 2 million procedures with fluoride-18. The number of moly/tech procedures increases between 2 and 5 percent each year. I don't know the numbers, but fluoride-18 procedures are progressing much faster than that.



D. Calma/IAEA

"We are living in a revolution of imaging...."

Fluoride-18 has to be produced close to the hospital because of its short half-life of 110 minutes.

Question: Is it possible to quantify medical isotope treatment of patients in life years?

AIPES is not an expert in this, but other organizations, like the EANM, the European Association of Nuclear Medicine, might have an answer.

If you have a heart problem and you have so-called perfusion imaging diagnostics, you will have five procedures during your lifetime, compared to a drug you take every day. Another well-known application in nuclear medicine, is using the fission product iodine-131 to treat thyroid cancer.

Question: What can you say about the future of nuclear medicine?

The main issue in nuclear medicine—treatment of disease—by far is the radioactivity toxicology, but the active ingredient we use to target the malignant organ is almost like homeopathy, an extremely low concentration of active ingredient....

It is clear that we are living in a revolution of imaging throughout the whole world. Imaging is becoming more and more important in diagnostics and medicine, and nuclear medicine is part of it.

Perhaps you have heard of personalized medicine. It is clear that each patient is different, even if they have the same disease, because of their specific DNA. Nuclear medicine allows you to create drugs that will target very specific molecules, personalizing the treatment with the help of molybdenum, technetium, or fluoride. These new radioisotope drugs are first tested on animals but will be available for human use soon. This is definitely a new world for nuclear medicine. Maybe in some cases you will be able to take a personalized drug after having had only a nuclear medicine imaging procedure. It could happen!