

# Curies for patients

*Many facilities in the world produce artificial radioisotopes, which benefit millions of people every day. By Lawrence Kidd*

**H**undreds of different types of radioisotopes are produced today, having multiple applications in medicine, agriculture and food production, and industry. A small number of key radioisotopes, produced in a small number of countries, dominate world production by value. The total value of less than \$500 million per year ascribed to world radioisotope production belies the importance of this vital step in creating the huge value derived from non-power nuclear applications.

## PRODUCTION METHODS

Unlike the radium applied by Marie and Pierre Curie, many of the radioisotopes used in today's applications are not extracted from materials occurring naturally in the Earth. Most are only found in very small amounts, due to many having only short half-lives. Some radioisotopes are also not found naturally, such as molybdenum-99, and therefore have to be created artificially.

There are essentially three ways of creating a radioisotope artificially. Firstly there is neutron gain, where an element is exposed to neutrons and an extra one is absorbed by the nucleus,

thus changing its atomic mass. The best example of this is cobalt-60 production: when cobalt-59, a stable isotope, is exposed to a high neutron flux, it can absorb another neutron and become cobalt-60, a radioisotope used frequently across all non-power applications.

The second way of producing radioisotopes is through fission, as first demonstrated by Enrico Fermi: the nucleus of an atom is forced to split and creates byproducts. This is the more common form of radioisotope production used today.

Thirdly, radioisotopes can be produced artificially *via* particle accelerators such as a cyclotron, by directing a proton beam at a target material to generate radioactive isotopes. Many commercial isotopes are produced this way.

## REACTORS

Most of the reactors used for radioisotope production are research reactors (see Table 1), but some power reactors are also used to produce radioisotopes (see Table 2).

The first reactors to produce radioisotopes as well as electricity were Candu reactors, after testing in research reactors in Canada. These reactors use nat-

ural, as opposed to enriched, uranium and in the core there is a high neutron flux – an ideal situation for neutron gain. Most frequently, cobalt-59 isotopes are placed in specially designed rods in the reactor core for approximately two years until the extra neutron is gained and it becomes cobalt-60. This operation takes up a minor amount of space in the reactor core.

## Research reactors

There are about 250 operational research reactors in the world, and of these about 100 produce radioisotopes for non-power applications of nuclear. Research reactors have very different power levels and are often multi-purpose facilities, so output of isotopes varies between them hugely.

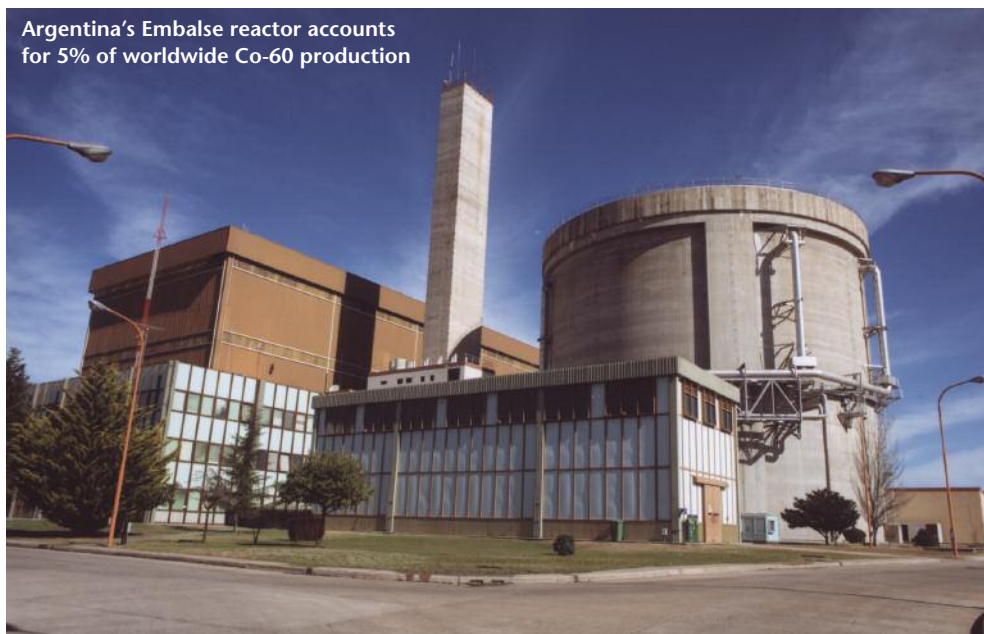
Research reactors can produce radioisotopes through fission, where radioisotopes are created as byproducts of the fission reaction. With the right temperature and speed of neutrons the fission of an atom can be controlled to split it into specific, desired radioisotopes.

Research reactors can produce more than one radioisotope at a time in their core, meaning that they are usually the most cost efficient way for countries to produce radioisotopes for non-power applications.

## Cyclotrons

A cyclotron particle accelerator uses a magnetic field to speed up different particles. Unlike power and research reactors it requires no uranium or fissionable materials to run. Particles are guided by the magnets round in a circle until they reach a desired speed, then magnets can force the particles onto a target and a nuclear reaction can take place. There are currently more than 300 cyclotrons producing radioisotopes in the world. The country with the most, by a distance, is the USA.

Unlike research and power reactors where there are other duties to perform, a large number of cyclotrons are built and run solely for the production of radioisotopes. However a downside



Argentina's Embalse reactor accounts for 5% of worldwide Co-60 production

**Table 1: Research reactors producing radioisotopes**

Country	Reactor name	Location	Type	Power (kW)	Country	Reactor name	Location	Type	Power (kW)
Argentina	RA-3	Buenos Aires	Pool	5000	Korea	HANARO	Taejon	Pool	30,000
Australia	OPAL	Lucas Heights	Pool	20,000	Libya	IRT-1	Tripoli	Pool	10,000
Bangladesh	TRIGA Bangladesh	Dhaka	TRIGA Mk II	3000	Malaysia	MINT TRIGA	Bangi	TRIGA II	1000
Belgium	BR-2	Mol	Tank	100,000	Netherlands	HFR	Petten	Tank in pool	45,000
Brazil	IEA-R1	Sao Paulo	Pool	5000	Nigeria	NIRR-1	Zaria	MNSR	30
Bulgaria	IRT Sofia	Sofia	Pool	2000	Norway	Jeep II	Kjeller	Tank	2000
Canada	NRU Slowpoke	Chalk River Edmonton	Heavy water Slowpoke-II	135,000 20	Pakistan	Parr-1	Islamabad	Pool	10,000
Chile	RECH-1	Santiago	Pool	5000	Peru	RP-10	Huarangal	Pool	10,000
China	HFETR MJTR	Chengdu Chengdu	Tank Pool	125,000 5000	Poland	Maria	Swierk	Pool	30,000
Czech Republic	LWR-15	Rez	Tank	10,000	Portugal	RPI	Lisbon	Pool	1000
Egypt	ETR-1	Inshas	Tank	2000	Romania	TRIGA ACPR	Pitesti	TRIGA II	14,000
Finland	FIR-1	Otaniemi	TRIGA II	250	Russia	BOR-60 VVR-Ts MIR-M1 SM IR-8 WWR-M	Dimitrovgrad Obninsk Dimitrovgrad Dimitrovgrad Moscow Gatchina	Fast breeder Tank Pool Tank Pool Tank	60,000 10,000 100,000 100,000 8000 18,000
France	Orphee Osiris	Saclay Saclay	Pool Pool	14,000 70,000	South Africa	Safari-1	Pelindaba	Tank in pool	20,000
Germany	FRMZ TRIGA Heidelberg II FRM-II	Mainz Heidelberg Garching	TRIGA II TRIGA Pool	100 250 20,000	Switzerland	AGN 211P	Basel	Homogenous	2
Ghana	Gharr-1	Legon	MNSR	30	Taiwan	Thor	Tsing Hua	TRIGA	2000
Greece	GRR1	Athens	Pool	5000	Thailand	TRR-1/M1	Ongkharak	TRIGA III	2000
Hungary	Budapest RR	Budapest	Tank	10,000	Turkey	TR-2	Cekmerce	TRIGA II	5000
India	Cirus Dhruva Apsara	Trombay Trombay Trombay	Heavy water Heavy water Pool	40,000 100,000 1000	UK	Imperial College	Ascot	Pool	100
Indonesia	RSG-GAS TRIGA II, Bandung	Jakarta Bandung	Pool TRIGA II	30,000 2000	USA	ATR HFIR MITR-II MNRC MURR NSCR OSTR Reed College Uni. Arizona TRIGA WSUR	Idaho Oak Ridge Massachusetts Sacramento Missouri Texas Oregon Portland Tucson Washington	ATR-LWR Tank Tank TRIGA II Tank in pool TRIGA TRIGA II TRIGA TRIGA TRIGA	250,000 85,000 5000 2000 10,000 1000 1100 250 100 1000
Italy	TRIGA RC-1 Lena TRIGA II	Rome Pavia	TRIGA II TRIGA II	1000 250	Uzbekistan	WWR-CM	Tashkent	Tank	10,000
Japan	JRR-4 TRIGA II Rikkyo JMTR JRR 3M	Tokai-mura Rikkyo Oarai Tokai	Pool TRIGA II Tank Pool	3500 100 50,000 20,000	Vietnam	Dalat VNR-01	Dalat	Pool	500

of using a cyclotron compared to a research reactor is that only one type of radioisotope can be produced at a time. This means that to change the radioisotope to be produced, the setup would have to be changed.

The split between the different production methods is unequal. Research reactors produce more radioisotopes than the other two main methods combined. In terms of value, power reactors are the second biggest producer of radioisotopes, with cyclotrons in third.

**Processing**

The raw radioisotopes produced at a reactor or cyclotron are normally sold to companies who turn them into useable, tradable items at their own processing sites. An example of

**Table 2: Power reactors producing radioisotopes**

Country	Reactor name	Location	Type	Power (kW)
Argentina	Atucha 1	Buenos Aries	Pressurised heavy water	357
	Embalse 1	Córdoba province	Candu	648
Canada	Bruce 5	Ontario	Candu	915
	Bruce 6	Ontario	Candu	915
Russia	Leningrad 1	St Petersburg	RBMK	1000
South Korea	Wolsong 1	Gyeongsangbuk-do	Candu	678.7
	Wolsong 2	Gyeongsangbuk-do	Candu	700

this is in Canada where radioisotopes are produced at the NRU research reactor and then processed at a plant owned by MDS Nordion in Ottawa, Ontario.

**RADIOISOTOPE PROFILES**

Across all non-power applications many different radioisotopes are used for hundreds of different purposes. To analyse the characteristics, value and

Over a quarter of Mo-99 isotopes are produced at the Joint Research Centre's High Flux Reactor in the Netherlands



production of each radioisotope individually is unnecessary, as most of the production (and value) focuses around a few core radioisotopes, widely used right across the world.

These key radioisotopes are:

- Cobalt-60.
- Molybdenum-99/technetium-99m.
- Thallium-201.

**Cobalt-60**

Cobalt-60 decays by beta particle emission and gamma radiation. It has a half-life of just over five years. It is produced through neutron gain, by placing rods of cobalt-59 in a power reactor or through fission in a research reactor. Major medical applications are in cancer therapy and the sterilisation of medical equipment. Cobalt-60 is also used in other sectors, notably food irradiation and materials testing.

An estimated 60 million curies of cobalt-60 are produced annually. Canada is by far the dominant producer, with Russia and Argentina also producing significant amounts (see Table 3). Production of cobalt-60 is not as widespread across the world as many other radioisotopes. India produces a small amount, as do Australia, China, Korea and the USA. Few countries produce enough to fulfil national demand and so rely on imports from Canada or the other two big producers.

**Molybdenum-99**

Molybdenum-99 decays to technetium-99m, its daughter radioisotope, by emission of beta particles and gamma radiation. It has a half-life of just under 66 hours. The vast majority of molybdenum-99 is produced in order to generate technetium-99m, a metastable nuclear isomer of technetium-99 that emits gamma radiation and has a half-life of six hours.

Molybdenum-99 is created by fission of uranium in a reactor. Technetium-99m can also be directly created in a cyclotron, though this is rare. A major application is as a tracer for multiple organs in diagnosis. Significant producers are Canada, the Netherlands, Belgium and South Africa (see Table 3).

Because of technetium-99m's key role in modern nuclear medicine and its short half-life, there are plenty of producers worldwide that dispatch to hospitals. In particular there is reasonably large production in France, Australia and China. Production in less developed countries is small due to lower demand and expenditure on medicine.

**Table 3: Producers of major isotopes**

<b>Cobalt-60</b> (Estimated worldwide production: 60 million curies)		
		Share of world production
Canada	NRU (research reactor) Bruce B (power reactor)	83%
Russia	Leningrad 1 (power reactor) Mayak reprocessing plant	7%
Argentina	Embalse 1 (power reactor) Atucha 1 (power reactor)	5%
Rest of world		5%
<b>Molybdenum-99/Technetium-99m</b> (Estimated worldwide production: 468,000 curies*)		
Canada	NRU (research reactor)	38%
Netherlands	HFR (research reactor)	26%
South Africa	Safari-1 (research reactor)	16%
Belgium	BR-2 (research reactor)	16%
Rest of world		4%

\*With 6 days of pre-referencing

**Thallium-201**

Thallium-201 decays by emitting gamma rays, and has a half-life of just over 72 hours. Its major application is in heart imaging. Thallium-201 is produced in cyclotrons and other particle accelerators, and because of this, there are no countries with large dominance in its production that export to the rest of the world.

The largest producers of thallium-201 are also its largest consumers. It is, for example, one significant radioisotope that the USA produces in volume due to the demand in its hospitals – it is usually supplied to the hospitals by local universities or commercial radioisotope producers.

**THE RADIOISOTOPE MARKET**

These three key radioisotopes – cobalt-60, molybdenum-99/technetium-99m and thallium-210 – dominate the overall market. Excluding these three, there is no other radioisotope that commands more than a \$10 million value (see Table 4).

**COUNTRY PROFILES**

The production of radioisotopes can also be analysed from a national perspective. In the radioisotope profiles in the previous section, it is clear that a few countries dominate world production. In terms of value of radioisotopes produced, three countries produce, and sell, a large percentage of the worldwide market: Canada, Russia and the Netherlands.

**Canada**

Since the *Atoms for Peace* movement began, Canada has been a leading country in research, investment in facilities and the production of radioisotopes. AECL is the company responsible for research, building, maintenance and operation of Canadian nuclear facilities. It has large-scale activity in both power and non-power applications. AECL designs and builds its Candu reactors across the world, as well as different research reactor designs.

In 1957, the NRU research reactor became operational, and was used mainly for research. Today, after some updating, it is the primary producer of Canada's radioisotopes. There are also smaller research reactors that produce much smaller quantities of radioisotopes, mainly for local use. AECL also uses some of its power reactors to produce radioisotopes.

Radioisotopes produced at both research reactors and power reactors are supplied to MDS Nordion, a world-

wide company that has exclusive rights to distribute the radioisotopes produced by AECL. The production of cobalt-60 by neutron gain in power reactors was pioneered by the two companies at the Pickering and Bruce sites.

Canada is comfortably the world's leading producer of all the major radioisotopes. Notably, it has dominance in cobalt-60 production where, because the radioisotope has such a long half-life, it has time to ship it out of the country to anywhere in the world. This is not possible, even with today's quick transportation methods, for the radioisotopes with shorter half-lives.

Canada has taken advantage of the failure of the USA to build radioisotope-producing reactors, so a large percentage of the income from exports comes from its neighbour. There was some debate 10 years ago about the USA investing in its own radioisotope production facilities, or using its existing reactors to produce radioisotopes, but it opted to continue to import from Canada. As well as to the USA, MDS Nordion sells various radioisotopes to over 60 other countries around the world. No other country in the world has such widespread distribution of radioisotopes.

**Russia**

Russia is the second largest radioisotope producer in the world. There are around 50 research reactors operational in the country, many of them built originally for military uses. Some of these reactors now help to produce radioisotopes. There is no one reactor

**Table 4: Estimated worldwide value of radioisotope production**

Radioisotope	Estimated value (\$ million)	Percentage of total value
Cobalt-60*	210	45.6%
Molybdenum-99**	117	25.4%
Thallium-201	55	12%
Others	78	17%
Total	460	

\*Based on an assumed world average price of \$3.50 per curie

\*\*Based on an assumed world average price of \$250 per curie

that produces the majority of radioisotopes like in Canada: instead production is much more evenly distributed across the country.

Over 60 different radioisotopes are produced in Russia. The radioisotopes are exported by Tenex (Techsnabexport) to many companies across the world, particularly China, USA, UK, Japan and Australia. Joint ventures such as Revisss (Russian-English Venture in Isotopes Supply Services) mean that there is security of supply to the different receiving countries.

As well as research reactors, there are also many cyclotrons in Russia that can produce radioisotopes, and one radioisotope-producing power reactor, the Leningrad 1 RBMK.

**Netherlands**

The Netherlands has played the leading role in Europe in radioisotope production for non-power applications. Dutch-based NRG is the largest supplier of radioisotopes to the European





Two units at Canada's Bruce B power station are used for radioisotope production

market and also performs experiments to continue to develop production.

The major source of radioisotopes in Holland is the HFR (High Flux Reactor) based in Petten. The reactor was built in 1957 and is owned by the European Commission as both a research and radioisotope production facility. The Netherlands' central location in Europe gives NRG good transport links right across the developed part of Europe, where the spending on healthcare, industry and crop development means the demand for radioisotopes is higher.

Although producing a significant amount of medical radioisotopes, the HFR does not produce radioisotopes such as iridium-192, which is often used outside of medicine.

### Other countries

After these three major countries, there is another group of countries that produces significant amounts of radioisotopes between them, but not enough to command a large total

share of the revenues individually. Belgium, South Africa and Australia would be considered in this group, with Belgium being the largest. All three of these countries have large research reactors that are used for radioisotope production (see Table 1).

### THE FUTURE

Nuclear techniques have developed at a very rapid rate. Even in the developed world 20 years ago, one would have been very lucky to receive diagnosis by a PET scan or another advanced form of nuclear medicine, and there is potential for continued growth in all areas of non-energy applications of nuclear.

The rise of nuclear medicine in the past century from the discovery of radiation and radium treatments, to the advanced scanning machines of today gives a glimpse of how different it may be in 50 or 100 years' time.

One thing that looks certain is that there will continue to be improvements in scanning techniques for diagnosis.

PET and CAT scans have been constantly redesigned improving the quality of the image for doctors to view. This has led to more accurate diagnoses and more effective treatments for patients.

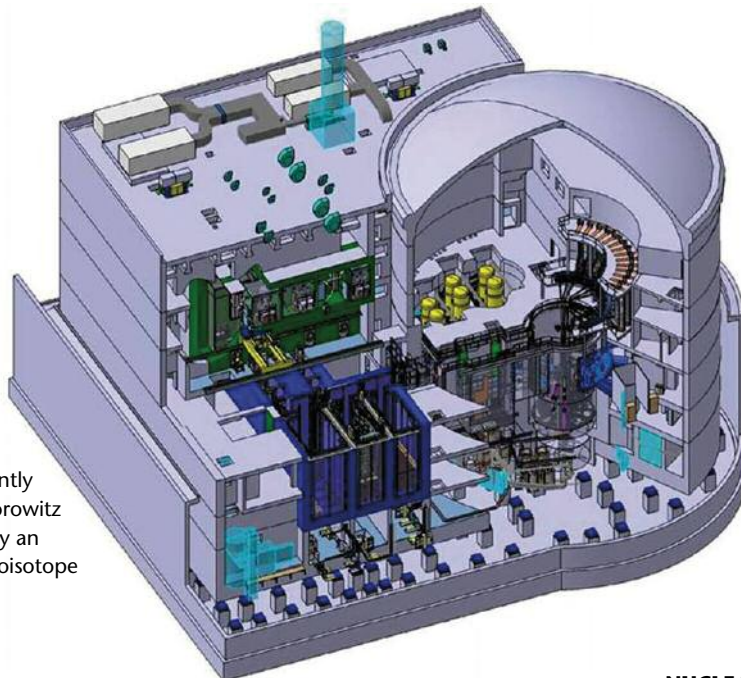
The demand for nuclear medicine seems set to rise not just in the developed world but in the developing world as well. Countries such as China are growing rapidly, and the standard of living for a large percentage of its citizens is improving. It seems inevitable that as countries get richer, more will be spent on healthcare and the treatment of diseases; nuclear techniques will have their role to play in this.

One area where there could be advances in the future is in treatments for the brain. The brain is the body's most complicated organ and treatments are, even today, not guaranteed to work. Better imaging and the ability to more precisely apply radiation to different areas could improve understanding of how the brain works and increase recovery rates for diseases such as brain cancer, depression and Parkinson's disease.

### Future production

The expected increases in uses of radiation from nuclear sources in the future will create a larger demand for radioisotopes to provide this radiation. Demand has increased considerably in the past decade. Using molybdenum-99 as an example, there has been an increase in demand of over 50% in the last ten years. Some predictions have suggested there could be as much as a 10% rise each year. An increase at this rate would see the demand for radioisotopes double in seven years' time, thus pushing the value of the market towards \$1 billion per year.

If demand increases without more facilities to supply radioisotopes, there



Construction has recently begun on the Jules Horowitz reactor, which will play an important part in radioisotope production in Europe

may be large price rises. To keep non-energy applications affordable and to benefit all, more radioisotopes must be produced to cope with the increases in demand. One response is to build more reactors.

In France, construction has started on a new research reactor – the Jules Horowitz reactor – which will play an important part in radioisotope production in Europe. Although not its primary role, it will be such a powerful reactor that it will be able to provide about a quarter of Europe's radioisotope demand, assisting Europe's other two major radioisotope producers in the Netherlands and Belgium.

A considerable setback occurred recently when, in May 2008, AECL announced that it was discontinuing work on its two-reactor Maple (Multi-purpose Applied Physics Lattice Experiment) radioisotope production facility at the Chalk River site. The two reactors, which had already been built and were undergoing commissioning, would have been the world's first reactors dedicated solely to medical isotope production and would have been capable of providing at least 100% of the world's current demand for molybdenum-99 and cobalt-60 used in medicine, as well as many other radioisotopes.

### Limitations to growth

How much the market for radioisotopes increases in the future will depend largely on how the perceived problems could be overcome. Two of the major limitations are concerns over transport and public perception.

The issue of transportation is not specific to non-power applications; it is an argument that has long been used by anti-nuclear protesters, originally against nuclear power plants. They argue that the transportation of radioactive materials could cause radiation leaks in the event of a crash or that the materials themselves could end up in the hands of terrorists. The International Atomic Energy Agency (IAEA) has worked on this for the whole duration of its existence and continues to provide strict guidelines for transportation of all radioactive materials.

All nuclear applications have the problem that the general public know very little about them. With the majority of press articles about radiation being negative, through, for example, radiation poisoning and use by terrorists, they fear it. Turning around this sort of public perception will not be easy, but such changes have been

## Early days of medical radioisotopes

The use of radioisotopes in medicine can trace its roots back to the earliest days of nuclear science. In 1901, Henri Alexandre Danlos and Eugene Bloch first used pure radium extracted from pitchblende to attempt to treat a tuberculous skin lesion. Pierre and Marie Curie also experimented with medical uses of radium extracted from pitchblende; during the First World War Marie Curie famously treated injured soldiers with radium. These early applications had varying levels of success. The Curies and Becquerel shared the 1903 Nobel Prize in physics for their discoveries, while Marie was also awarded the 1911 prize in chemistry for her efforts in the extraction and investigation of the properties of radium.

Radium therapy was big business. Thousands of tons of pitchblende were needed to extract just a few grams of radium. Scientists paid the equivalent in today's money of up to \$10 million for just 1g of radium. It was by far the most valuable substance in the world. The medical benefits of radium were vastly overstated while the dangers of radiation were not yet known. Handlers often received burns caused by the radiation and it is suspected that many researchers died because of exposure to it.

In 1923 the first tests using radiation as a tracer to follow blood flow were performed. The use of radioactive tracers began the process that would be used in the future for medical diagnosis as well as in many areas of industry and agriculture, which could not have been foreseen at the time.

In 1934 Irène and Frederic Joliot-Curie created 'artificial' radioactivity by bombarding aluminium with alpha particles to create a radioactive isotope of phosphorus. This was the achievement that many scientists had been waiting for as it led to the availability of cheap radioactive elements in sufficient amounts for research and other applications. The cyclotron, invented by Ernest Lawrence in 1929, would prove vital for the creation of new radioisotopes. The first cyclotron built specifically to create radioisotopes for medical purposes was opened at Washington University in 1940.

Then came the Second World War, and although huge advances were made in atomic science, studies of peaceful nuclear applications were largely put aside in the race to create nuclear weapons. President Eisenhower's landmark *Atoms for Peace* speech to the United Nations General Assembly in 1953 helped signal a change in the perception of nuclear energy. Governments began to recognise the possibilities and benefit to humanity that nuclear technologies could bring, assuming cooperation between the worlds' scientists, who had previously largely worked in small, secretive groups.

The increased demand for radioisotopes in the wake of *Atoms for Peace* led to the building of research reactors. These small reactors, often located on university campuses, operate at much lower temperatures and use less fuel than the large reactors used for energy. Materials inside the reactor can be bombarded with neutrons. These reactors were built to find new radioisotopes, and to create radioisotopes for research and for sale to hospitals and other institutions. Abbott Laboratories were pioneers in the distribution and sale of radioisotopes, selling the first one, an isotope of iodine, in 1950.

### LATER DEVELOPMENTS

In nuclear medicine, great progress was made during the middle decades of the 20th Century and several new radioisotopes were experimented with. Iodine-131 was used in diagnosis and treatment of thyroid cancer and other diseases; phosphorus-32 was used to detect brain tumours and treat leukaemia; and sodium-24 was also used for the first time in leukaemia treatment. Throughout this era the newly-created radioisotopes were being used to diagnose and treat different diseases, some with great success. No radiopharmaceuticals were being used outside of laboratories until 1951, however, when the US Food and Drug Administration (FDA) approved I-131 for use with thyroid cancer patients. Gradually after this, more radiopharmaceuticals were allowed in public hospitals.

The very advanced scanners that are seen today in nuclear medicine have developed over the past half century from much more basic versions. Positron Emission Tomography, also called PET imaging, can be used to diagnose many diseases including cancer. It works by emitting and recording positive beta decay to form a three-dimensional view of the body which can be used to diagnose diseases. Computerised Axial Tomography, CAT or CT scans work in a similar way but use X-rays to create a picture of the body.

Another product of *Atoms for Peace* research in the medical industry is sterilisation. Most types of medical equipment from syringes to contact lenses can be sterilised with gamma radiation from a cobalt-60 source to kill bacteria. This technique was first introduced in the late 1950s and today is common practice across most of the world.

achieved in the past. For example, there was a time when there was a large public outcry against the pasteurisation of milk, but now the benefits in destroying bacteria from milk have become almost universally accepted. Secondly, the fluoridation of water, which demonstrably benefits tooth care, was originally strongly opposed.

Other limitations are human resources/infrastructure and safety. Nuclear applications are advanced technologies that require expertise and a technological infrastructure to support them. A PET machine, for example, needs highly trained operators, doctors who know how to interpret the results, and sufficient energy and other

infrastructure to run. It cannot simply be dropped into a hospital in a developing country. Also, all nuclear applications require well-developed regulatory structures to ensure their safe use, given the potential dangers to humans of uncontrolled radiation exposure. So, both training and education to build a qualified nuclear workforce and government safety regulations and enforcement mechanisms must be in place in a country in order for the use of nuclear applications to grow, and most of the world's countries are still lacking in these. ■

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