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Some important applications of accelerators in medicine and industry

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Abstract. Accelerators, and cyclotrons in particular, have long been dedicated to research. Nowadays, they are industrial devices heavily used in various fields. The Belgian company Ion Beam Applications, probably the largest private company manufacturing cyclotrons, has largely contributed to the dissemination of this technology into the medical and radio-pharmaceutical community. This paper will present different applications of cyclotrons in these fields, from radioisotope production to radiotherapy, based on IBA's experience since 1986, date of construction of the CYCLONE 30 prototype, a cyclotron that revolutionised cyclotron technology for medicine and industry. Possible industrial applications of cyclotrons will also be mentioned, together with applications of another type of accelerator recently introduced in the market by IBA: the Rhodotron.

1. Introduction

IBA is a spin-off of the research centre for cyclotrons of the Catholic University of Louvain, in Louvain-la-Neuve (Belgium). In 1985, the accelerator research team of the university developed the design of a high extracted beam intensity, low power consumption H^- cyclotron for the production of medical radioisotopes. The design was extremely innovative in many respects, and a patent was filed by the university. Facing the difficulty to find local industries interested in further developing this new cyclotron concept, the decision was taken, in 1986, to start a small private company to develop the new technology and to industrialise and sell the new cyclotron design. Today, with 90 employees and 35 accelerators sold, IBA is probably the largest private company manufacturing cyclotrons [1]. Since 1986, IBA has diversified into 4 different markets - radioisotope production, Positron Emission Tomography (PET), radiotherapy, and sterilisation & industrial irradiation - and has developed accelerator-based systems for various applications. The present paper is based on this experience.

2. Cyclotron-based production of radioisotopes for nuclear medicine

Cyclotrons were used first for fundamental research in nuclear physics. Today they are used for studies in a variety of other disciplines and are also heavily used in various production processes, for example for the production of medical radioisotopes.

2.1 Radioisotopes for imaging and diagnosis in nuclear medicine

Radioisotopes are now essential in diagnosis and study of the human functions and are at the basis of the fast growth of imaging in nuclear medicine. They allow to study the functions of parts of the human body and to take pictures of organs that can not be represented in another way. In fact, radioisotopes injected in the human body produce weak radiation that can be read, for example, by gamma cameras. Various radioisotopes are produced [2], according to the organ that must be represented. They include Gallium 67 (used in cancer and hidden infection diagnosis), Iodine 123 (used for all in-vivo studies of the thyroid), Thallium 201 (used in patients with heart disease), Krypton 81m (for diagnosing the threat of pulmonary embolism), Mercury 195m (for blood flow rate studies), among others.

The access to the full range of radioisotopes used in nuclear medicine is vital to the early diagnostic and treatment of a wide variety of problems including cancer and heart disease. To produce such radioisotopes, a medium energy cyclotron is a suitable device. In Europe, in the USA and in Japan, commercial companies operate cyclotrons to produce radioisotopes that they market themselves. All these commercial companies operate several cyclotrons in the same facility. Many important hospitals and clinics are now also equipped with cyclotrons producing radioisotopes for their own use or for a distribution on a regional scale. This is possible because the half-life of these radioisotopes is expressed in half-days so they can be transported over a reasonable distance. Remote countries, like Australia or Iran for example, too far to be serviced by these companies, are also equipping in cyclotrons.

This evolution was possible because of the high degree of automation, reliability and simplicity characterising the cyclotrons used nowadays for radioisotopes production. The CYCLONE 30 cyclotron produced by IBA is the world standard for radioisotope production [3]. It is a 30 MeV, fixed-field, fixed -frequency, dual extracted beam, H- cyclotron. Cyclone 30 is a very reliable, fully automated push-button system, with minimal activation of the machine and minimum radiation exposure for the personnel thanks to the H- technology. It was designed to give high extracted beam intensities (up to 500 μA) while keeping the power consumption very low (less than 100 kW with a 15 kW extracted beam). Since 1986, sixteen CYCLONE 30s have been manufactured and are in routine operation at radioisotopes production plants and in research centres around the world.

2.2 Increasing demand for high beam intensities

These characteristics, in particular the extracted beam intensities, were up to now well adapted to the production constraints, in particular from the point of view of the maximum current the targets may support. However, recent developments in target technology are at the root of an increasing interest, from the radioisotopes producers, for higher beam intensities. In parallel, there have been important progress in negative ion source technology. In this field, IBA is working in collaboration with AEA Technology, Culham, in the UK.

As a consequence, IBA is able today to propose an intensity upgrading system allowing a significant increase of the beam intensity of any existing Cyclone 30. This system includes a new, 7 mA H^- cusp ion source (or a 25 mA source, depending on the final current to be achieved) and a new RF amplifier. In some cases, it may also include a new injection line and/or a vacuum upgrade. A flexible installation program is foreseen in order to minimise the unavailability of the machine during the implementation of the upgrade. For the radioisotopes producers, the main advantage of this option is that the isotope production rate of their existing CYCLONE 30 can be increased while keeping unchanged the production facility (no need for an important investment in a new building) and most of the cyclotron operation costs (no need for additional personnel for example). Alternatively, this may be a way of reducing operation costs. Finally, high beam intensities may be needed for new cyclotron-based production of radioisotopes (see paragraph 2.3).

In parallel, for potential customers interested in a new machine, IBA is now marketing high intensity versions of Cyclone 30 in addition to the standard version. As well as for the intensity upgrades, extracted currents of up to more than 2 mA are proposed today.

2.3 *The particular case of ^{99m}Tc*

As mentioned in paragraph 2.1, gallium 67 and thallium 201 are among the most common medical radioisotopes produced with cyclotrons. However, the most frequently used radioisotope for nuclear medicine is produced with nuclear reactors: technetium 99m, which is distributed as ^{99}Mo => ^{99m}Tc generators. ^{99}Mo can be produced in nuclear reactors either by neutron activation on a natural molybdenum target through the reaction ^{98}Mo(n,γ)^{99}Mo, or by neutron induced fission on highly enriched uranium 235 via the reaction ^{235}U(n,fission)^{99}Mo. The last reaction is the preferred one as higher production yields and higher specific activities are obtained. Most of the nuclear reactors used for this production are due, in the next years, for a major refurbishment or for decommissioning. The problem of the future availability of nuclear reactors suitable for ^{99}Mo production - a fission product of ^{235}U - has prompted a renewed interest on alternative production methods. Two possible alternative production methods are presently under development: one of them is based on the direct accelerator production of ^{99m}Tc or ^{99}Mo, the other one is the proton-driven fission neutron source for the production of fission ^{99}Mo as proposed by IBA in collaboration with SCK-CEN, Mol, in Belgium (see [4,5] and paragraph 6.). Both methods require the use of high intensity cyclotrons.

As far as the direct accelerator production of ^{99m}Tc or ^{99}Mo is concerned, three possible cyclotron production techniques (one for ^{99}Mo and two for ^{99m}Tc) are currently being investigated [6]:

a) the low energy (20 MeV) production of ^{99m}Tc through the ^{98}Mo(p,γ)^{99m}Tc reaction,
b) the medium energy (40 MeV) production of ^{99m}Tc via the ^{100}Mo(p,2n)^{99m}Tc reaction,
c) and the high energy (70 MeV) proton-induced fission on ^{238}U targets to produce ^{99}Mo.

The technical feasibility of these alternative production methods is still being evaluated. Among others, there are questions regarding the specific activity of "instant Tc" and the separation chemistry of ^{99}Mo. There are also some practical questions to be addressed regarding the licensing process and the distribution logistics for "instant Tc". Nevertheless, some results of these investigations are very encouraging and, in the future, directly produced Tc could become a product complementary to generator produced Tc. In this case, the most promising methods will require high intensity proton beams, in the 2 to 5 mA range.

As far as the production of fission ^{99}Mo is concerned, the IBA proposal (see also paragraph 6.) is based on a 150 MeV, 1.5 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. The proposed accelerator is a cyclotron of the same kind than the high intensity, low energy, cyclotrons proposed by IBA to industrial producers of radioisotopes. It includes most of the advanced fundamental characteristics of these cyclotrons, in particular the negative ion technology. The accelerated particles are H- ions and the extraction is made by electron stripping on a thin carbon foil. This technology, well known by IBA, allows for a 100% extraction efficiency. This machine will take advantage of the experience on high efficiency RF power amplifiers developed for the Rhodotron accelerators (see paragraph 7.), of the experience of Cyclone 18+ on high beam power conversion efficiency (see paragraph 4.), of the experience with the high intensity versions of Cyclone 30, and of the above-mentioned development of the 25 mA H^- ion source with AEA Technology.

3. Cyclotrons specifically designed for Positron Emission Tomography centres

Positron Emission Tomography (PET) is a powerful diagnostic tool at the forefront of modern medical imaging. PET images biological function and physiology instead of anatomy. It uses short-lived radioactive isotopes (^{11}C, ^{13}N, ^{15}O, ^{18}F) which can be produced by low-energy cyclotrons (<20 MeV) accelerating protons and/or deuterons.

The CYCLONE 30 (see 2.) may be used to produce the radioisotopes needed for PET, and in fact some of them are used for this purpose but also for the production of other radioisotopes used in nuclear medicine. However, the very short life-time (a few minutes half-life) of most radioisotopes used in PET makes convenient and appropriate to place the isotope production equipment very close to the scanners. For centres using exclusively the PET technique, a CYCLONE 30 cyclotron would probably not be appropriate because they would use only a small part of its possibilities. IBA has therefore developed a range of turn-key systems which, in addition to cyclotrons, include targets and automated chemistry modules, and specifically cover each segment of the PET market. Most IBA's cyclotrons for PET inherit the best features of the CYCLONE 30 model [7].

The CYCLONE 3 is an extremely compact, easy to operate system for the production of the positron-emitting radio nuclide ^{15}O through the exothermic (d,n) reaction on natural nitrogen. It is a 3.8 MeV positive ion cyclotron designed for easy operation and reliability. The magnet cross-section is square, with a vertical acceleration plan, allowing the cyclotron structure to be used as shielding. The extraction is performed by means of an electrostatic deflector. Typical external beam intensity is around 50 μA. This cyclotron is ideal for centres mainly interested in production of ^{15}O for a number of blood flow studies, and that can obtain ^{18}F-FDG (also very useful for PET) from a radioisotopes distribution centre.

CYCLONE 10/5 is a self-shielded 10 MeV proton / 5 MeV deuteron cyclotron dedicated to the production of the most frequently used PET isotopes. This cyclotron is equipped with two internal sources permanently installed in the cyclotron, one for H^-, the other for D^- ions. The extraction of ions from CYCLONE 10/5 is done by the stripping method. Up to eight targets are located internally, i.e. inside the circular return yoke of the magnet which serves as a primary neutron and gamma ray shield. This cyclotron is oriented towards the clinical environment.

CYCLONE 18/9 (18 MeV proton, 9 MeV deuteron) allows large quantity production of all radioisotopes currently used in PET. It is also equipped with two negative ion sources, and the extraction is done by the stripping method. Targets can be located either internally or externally. This cyclotron has been designed to meet the special requirements of regional radioisotopes distribution centres, or medical research institutions which use $^{18}F_2$ (requiring a deuteron beam of minimum 6 MeV) and large amounts of ^{11}C.

Today, fifteen centres around the world have selected PET cyclotrons from IBA for clinical and research purposes.

4. Production of radioisotopes for therapy (brachytherapy)

Medical radioisotopes are generally used for imaging and diagnosis in nuclear medicine. But some of them are used for cancer therapy. Radioisotope production for therapy applications may require high intensity cyclotrons. In 1992 IBA was asked to develop a very high intensity, 18 MeV cyclotron for the production of the radioisotope ^{103}Pd. This radioisotope is marketed, in small sealed sources, for the local treatment of prostate cancer by the company Theragenics. It can be produced by a (p,n) reaction on Rhodium, a good material for internal target. However, the reaction yield is low and large beam currents are needed to achieve the desired production levels.

The development of this cyclotron by IBA, the CYCLONE 18+, was a new step in the evolution of cyclotrons for radioisotope production, in particular from the maximum intensity point of view. Indeed, since January 1993 CYCLONE 18+ operates continuously at 2 mA beam on target (twice the specification required by the customer). It is therefore demonstrated today, experimentally, that a cyclotron with an internal target can operate routinely at 2 mA beam current. Also 5 mA currents have been observed, and space charge calculations made for cyclotrons that do not require turn separation indicate that the intensity limit is probably around 10 mA average beam current [8]. This applies not only to positive ion cyclotrons using an internal target but also to negative ion cyclotrons where the extraction is made by charge exchange.

5. Cyclotrons for radiation therapy

5.1 Proton Therapy

The advantage of protons in radiation therapy, especially their ballistic accuracy, is widely acknowledged. However, the development of proton therapy as a clinical tool has been hampered by the complexity, the size and the cost of proton therapy facilities. Indeed, the medical use of protons require high energy accelerators not adapted, up to now, to the hospital environment. Pioneering institutions had to work with complex, inadequate equipment designed for research in nuclear physics.

IBA has integrated the technologies developed for its low and medium energy cyclotrons into a high energy system dedicated to proton therapy. The objective was to meet all the clinical specifications of a state-of-the-art proton therapy facility in the most simple, reliable and cost effective manner. The main elements of the IBA integrated system are the following [9]: a compact 235 MeV isochronous cyclotron, a short energy selection system transforming the fixed energy beam extracted from the cyclotron into a variable energy beam, one or more isocentric gantries fitted with a nozzle, a system consisting of one or more horizontal beam lines, a global control system including an accelerator control unit and three independent but networked therapy control stations, a global safety management system independent of the global control system, and a robotic patient positioning system.

In May of 1994, the Massachusetts General Hospital (MGH) of the Harvard Medical School in Boston, MA, USA, a pioneer in proton therapy since 1959, selected IBA to supply the proton therapy equipment of its new Northeast Proton Therapy Centre.

5.2 Neutron Therapy Systems

Neutron therapy may be more effective than conventional radiation for certain advanced tumours because it has the propensity to kill tumours cells which are low in oxygen and often become resistant to the usual forms of radiation.

IBA has a long track record in the design and development of equipment integrated in the Neutron Therapy Facility of the University of Louvain (UCL), an innovator in the field. This experience was instrumental in the conclusion of an agreement for marketing the Neutron Therapy System developed by Dr. Blosser at the Michigan State University. This system consists of an ultracompact, supraconducting, 50 MeV-deuteron cyclotron which rotates around the patient [10]. The neutron beam is produced by the (d,Be) reaction on an internal Beryllium target. A prototype is in operation at Harper Hospital in Detroit, MI, USA.

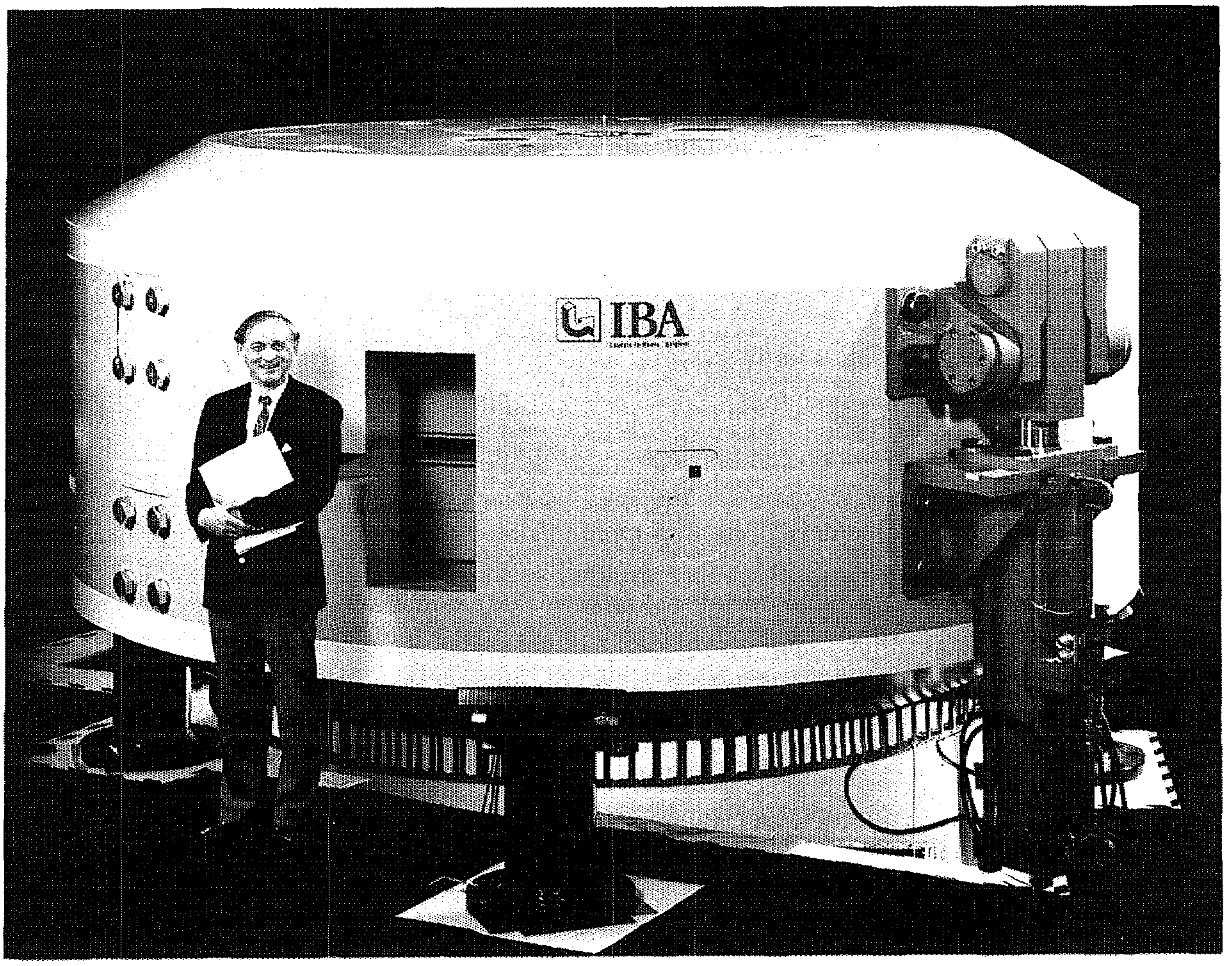

Figure 1. The 235 MeV isochronous cyclotron for proton therapy.

6. Neutron sources for radioisotope production, research and industrial applications

To replace the ageing nuclear reactors used for research, industrial applications, and radioisotope production, IBA, in collaboration with SCK-CEN, proposes the use an accelerator based spallation neutron source, with neutron multiplication by fission.

The proposed production system includes the following elements [4,5]:

1) a cyclotron able to accelerate 1.5 mA of beam at 150 MeV with low acceleration losses and almost 100% extraction efficiency;
2) a beam transport system, transporting the proton beam without losses to one of several possible neutron sources;

3) a primary target, made of molten Pb-Bi, where the proton beam produces spallation (mostly evaporation) neutrons. The expected neutron yield at 150 MeV is about 1 primary neutron per incident proton;
4) a water moderator surrounding the primary target;
5) a number of secondary targets made of highly enriched ^{235}U and located in the water moderator, at a close distance from the primary spallation target. Because the mass of ^{235}U is strictly subcritical, and arranged so as to produce the highest possible reactivity, any perturbation to the system will reduce the reactivity. The mechanical layout of the system will be such that the introduction of additional targets will be a mechanical impossibility.

Typical thermal neutron fluxes at the targets location should be around 2 10^{14} n/cm².s, which is similar to what is obtained in nuclear reactors used in these fields. But the non-critical nature of the system will make it more acceptable for the public than a nuclear reactor and should simplify the licensing process. Price, cost of operation, of disposal of radiowaste and of decommissioning should also be advantageous compared to nuclear reactors.

7. Sterilisation and industrial irradiation

During the last two years, with the Rhodotron, IBA entered also the field of high energy, high average beam current electron accelerators for sterilisation and other industrial applications. This new accelerator concept, developed by the team of Professor Pottier at the CEA in Saclay (France), was licensed to IBA. IBA started the development of a 10 MeV, 100 kW Rhodotron. The prototype completed successfully the beam tests at the end of 1994 and is presented in detail in [11]. Three Rhodotrons were sold in 1995.

Rhodotron accelerators are based on an innovative concept of using a single "re-circulating cavity" to provide high energy (up to 10 MeV) / high power (up to 200 kW) electron beams, with high electrical efficiency.

Such design makes it possible to achieve CW acceleration of electron beams to high energies. Rhodotron models open the doors to industrial applications for which high energy and high current electron beams are needed: crosslinking of plastics, sterilisation of medical products, polymerisation of composite materials, etc.

8. Ion beam techniques for material analysis and other industrial applications

Radioactive elements produced by cyclotron-delivered ion beams are at the basis of a number of techniques for analysis of industrial equipment, solids and thin films. One example is the measurement of degradation processes, like wear and corrosion affecting mechanical parts of machines, engines and industrial equipment. It is based on the activation, by an ion beam, of a well delimited area located on the surface of the mechanical part to be monitored. The depth of the activated zone and the resulting radioisotopes are carefully determined in accordance with the type and duration of the measurements to be performed. The level of radiation is extremely low and causes no alterations to the physico-chemical properties of the material. The mechanical part is then mounted onto its machinery and monitored by a measuring device designed to detect the gamma rays emitted from the labelled area. Once the machinery resumes operation, the wear and corrosion process begins, causing loss of material. This loss entails changes of radioactivity in the labelled area. These changes are detected and converted into measured values. Another means of measuring is to monitor the increasing amount of radiation in the lubrificant due to the loss of material from the activated area. Whichever method is applied, the precision is in the order of 1/10 of a micron. It is a non-destructive measurement system carried out on-line under real conditions. The method covers a wide range of application, among others in the automobile industry, the aircraft industry, and the chemical, petrochemical and power industries [12].

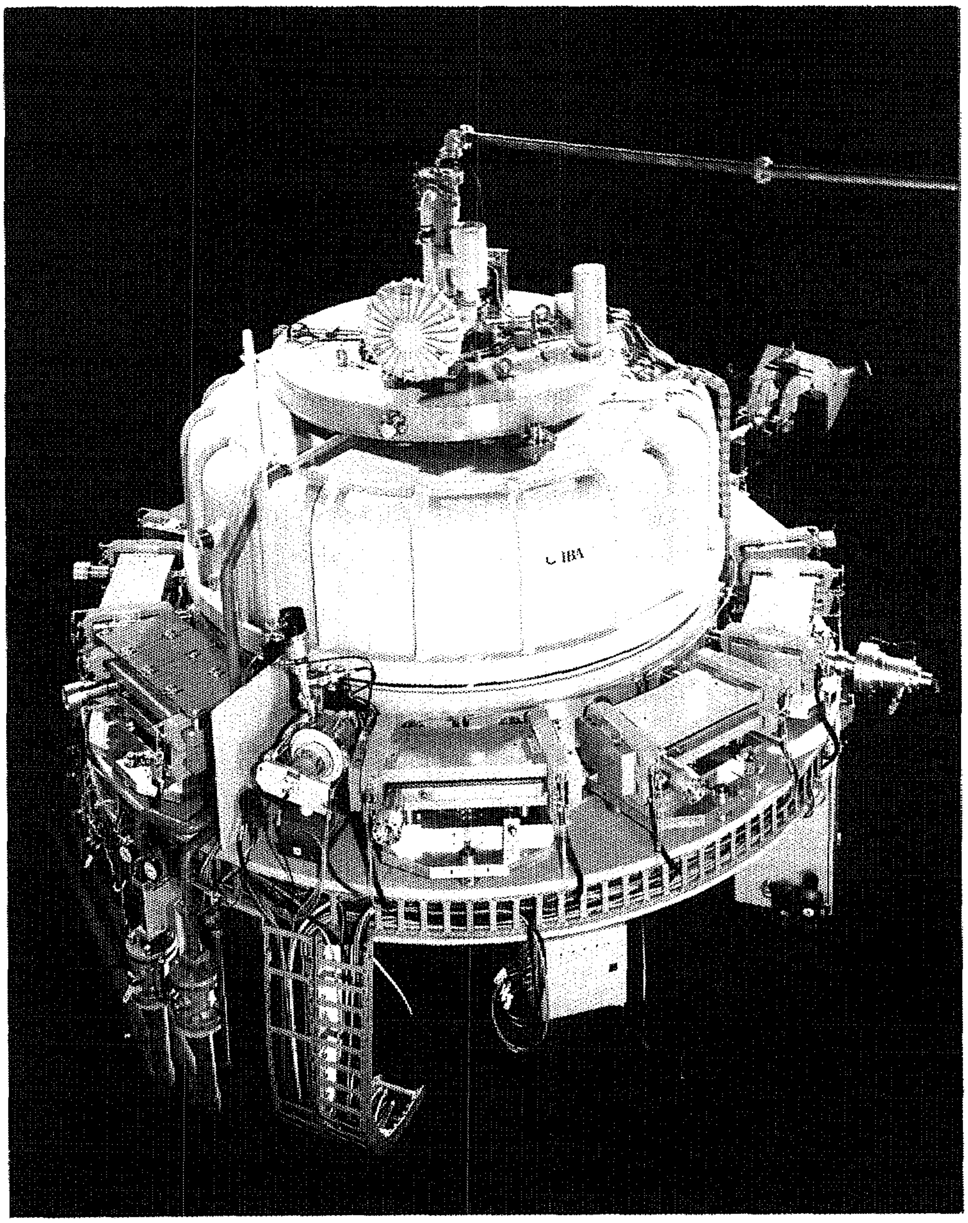

Figure 2. **The Rhodotron, a high power electron accelerator for sterilisation and other industrial applications**

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