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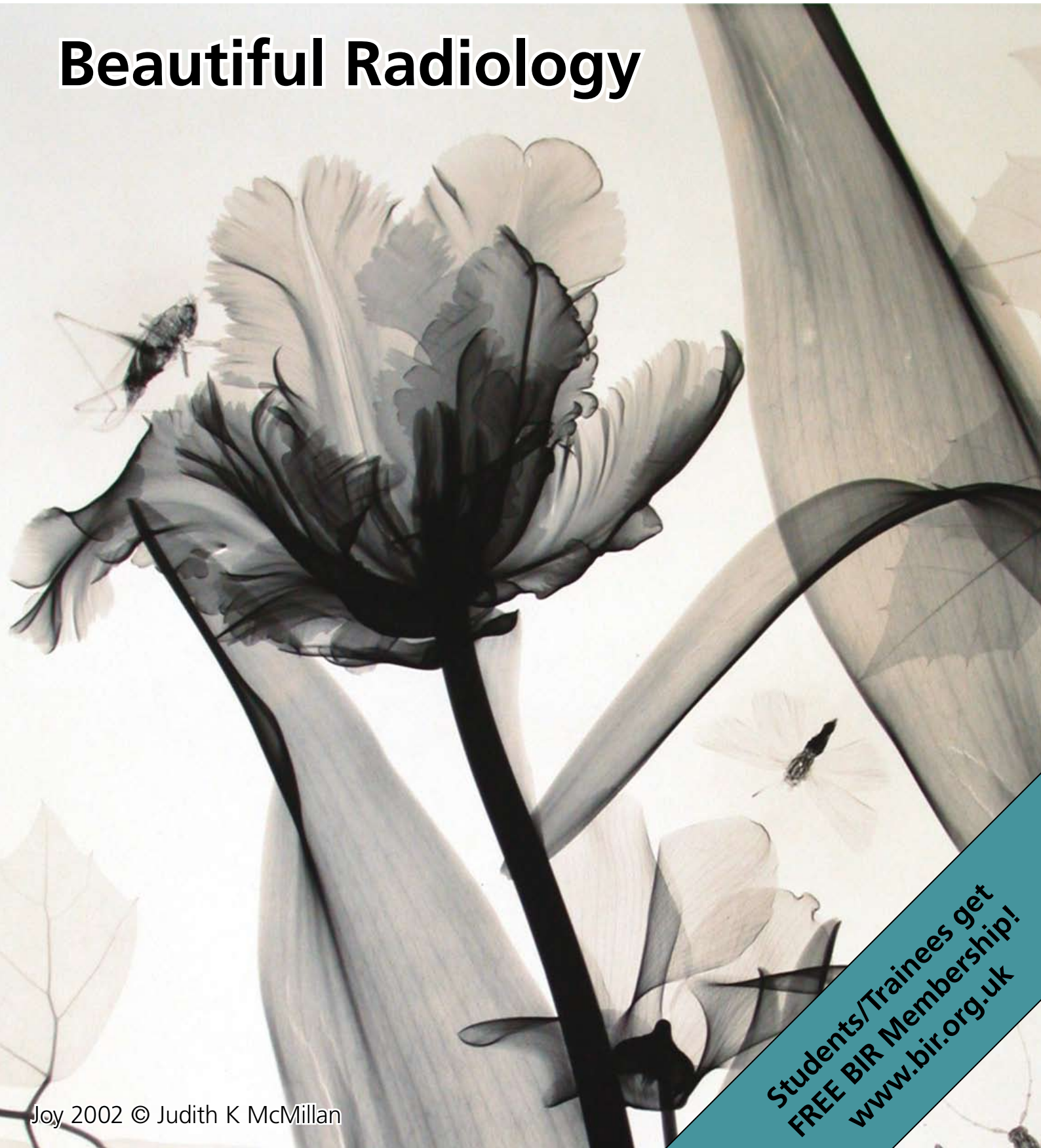
Beautiful Radiology



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Xenon MRI: New perspectives for molecular imaging

On the path to realization of the vision of personalized, targeted molecular therapies, diagnostic imaging plays a key role and makes molecular imaging (MI) a rapidly expanding discipline. Several challenges arise when entering this new dimension of radiology. The ideal molecular imaging technique should be of high spatial and temporal resolution, and use probes of high specificity and affinity to detect relevant cellular processes at nanomolar concentrations.

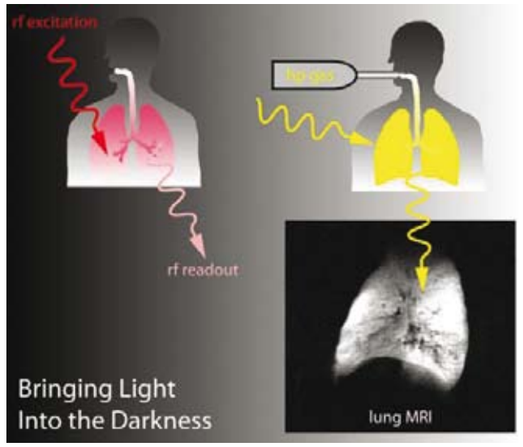

Figure 1: Following radio frequency (rf) excitation, the signal that is detected in conventional MRI is very weak and requires a high density of the nuclear spins. Imaging of void spaces can be realized by using hyperpolarized (hp) noble gases that benefit from a much higher detectable magnetization. In this example, helium imaging of the lung was one of the early applications of hp gases in biomedical studies. (Lung MRI reproduced from Magn. Res. Med 1996; 36: 192–196 with permission of John Wiley & Sons, Inc.)

Overcoming MRI's ancient sensitivity problem:

As an imaging method, MRI has significant advantages in terms of its non-ionizing character, unlimited penetration depth and high spatial resolution. However, the inherent low sensitivity is a major drawback that limits the detection to concentrations of ca. 10^{-4} moles per litre [1]. Conventional MRI-based MI approaches are further limited in their contrast because they measure relatively small changes in the dominant tissue water signal that arise from the presence of a targeted MI relaxation agent. Several years ago, introduction of hyperpolarized gases such as helium and xenon provided a convenient solution for imaging of areas where high spin densities of ^{1}H are not available, i.e. in diagnostics of the respiratory pathways (Figure 1) [2]. Combining the dramatic sensitivity gain of hyperpolarized media with the high specificity of the xenon nuclear magnetic resonance (NMR) signal makes ^{129}Xe an ideal nucleus to probe the molecular environment at the cellular level, even if the achievable spin density of this exogenous species after inhalation or direct injection via carrier solutions (Figure 2) is quite low in living tissue. Initial biomedical applications of xenon NMR included functional studies of uptake dynamics in different tissue types [3], angiography studies [4], brain imaging [5] and diffusion measurements from blood plasma into erythrocytes [6]. The conceptual novelty of xenon biosensors [7] was the subsequent pivotal step to relate the NMR signal of this inert element to specific molecules. Xenon biosensors function by dynamic encapsulation of the xenon nuclei in a molecular cage that is linked to a targeting moiety, such as an antibody. When encapsulated, xenon has a unique NMR signal allowing for the information from a specific binding event to be transferred to the encapsulated xenon, thereby providing molecular contrast in the final xenon image.

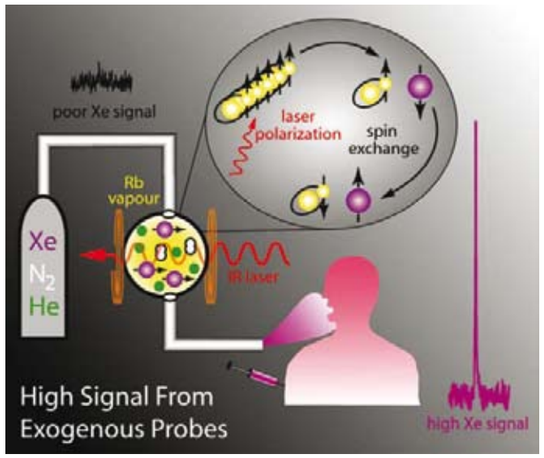

Figure 2: Hyperpolarized xenon is produced is the presence of rubidium (Rb) vapour that is exposed to infrared (IR) laser light for alignment of the electron spins of the alkali metal. This polarization is then transferred onto the xenon nuclear spins and gives a large NMR-detectable signal. Application to the patient can be realized via inhalation of the noble gas or injection of xenon-bubbled solutions.

Smart sensor probes for molecular contrast:

These xenon biosensors have two important features that are crucial for making MRI a powerful MI method. First, virtually any molecular target for which an affinity agent is known can be addressed with such

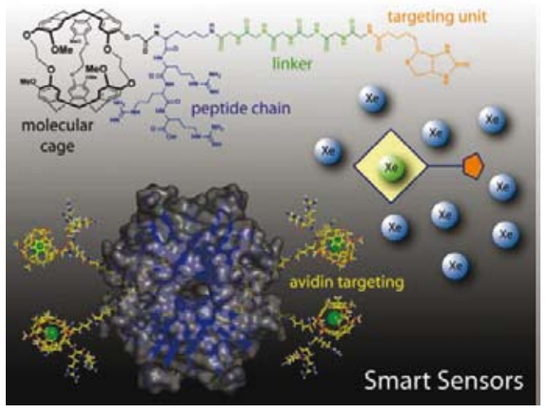

Figure 3: Key elements of xenon biosensors are the molecular cage to host the noble gas and the targeting unit to interact with the biomolecule to be detected. The cage "activates" the xenon nuclei by inducing a significant frequency shift, making them easily distinguishable from the atoms outside the biosensor. Sensors functionalized with biotin can target the protein avidin with biochemical specificity.

"tailored" probes. Second, these "smart" sensors activate the probe nucleus by endowing a unique resonance frequency (chemical shift) on xenon atoms when residing in the biosensor's molecular cage. Additionally, a new signal can appear in the presence of the intended target. It is therefore possible to distinguish at least three different xenon signals that provide information about the spatial distribution: the perfusion medium carrying the xenon, the inactive contrast agent that was delivered to a specific region of interest, and the activated sensor that accumulates in the type of targeted pathology. The chemical shift values of caged xenon can vary significantly with changes in the biosensor structure elements, such as the cage, linker and targeting moiety (Figure 3). Hence, many different "colours" of xenon biosensors can be employed to detect multiple targets simultaneously. This option for multiplexing is made possible by the outstanding chemical shift range of ^{129}Xe and the modular construction of the biosensor. The fact that the nuclei that are finally detected are not covalently bound to the contrast agent enables accumulation of one or more sensor types in the tissue prior to delivery of the hyperpolarized "spy nuclei" that have a much higher diffusivity.

HYPER-CEST: a unique way to store molecule-specific information:

Although the use of hyperpolarized nuclei represents a significant signal amplification, the xenon biosensor concept alone does not compare with the low detection thresholds (10^{-9} – 10^{-12} M) of radionuclides. Using commercially available polarizers, direct detection of the sensor signal still requires long measurement times due to extensive signal-averaging to image moderate concentrations (10^{-6} M). However, the enormous chemical shift allows for signal amplification based on an indirect detection method called HYPER-CEST. The chemical exchange of xenon nuclei in and out of the biosensor cage is characterized by ideal dynamic conditions: it is slow enough to resolve the two resonances of xenon encapsulated by the biosensor cage and xenon dissolved in the bulk solution, but fast enough to cycle many xenon atoms through the cages in a relatively short period of time. HYPER-CEST works by labelling several batches of xenon atoms that enter and exit biosensor cages, allowing sensor-related signal to accumulate in the large reservoir of solution-dissolved xenon. The xenon atoms transiently hosted by biosensor cages are selectively labelled using a radiofrequency pulse that erases, or "saturates", the magnetization of sensor-bound xenon (Figure 4). Because nuclei cannot naturally return to their hyperpolarized state after saturation, the sensor-derived information is effectively stored as a decrease in the overall signal of solution-dissolved xenon. This information is read-out by obtaining an MRI dataset of the dissolved xenon signal before and after selectively erasing xenon atoms hosted by biosensor cages. The

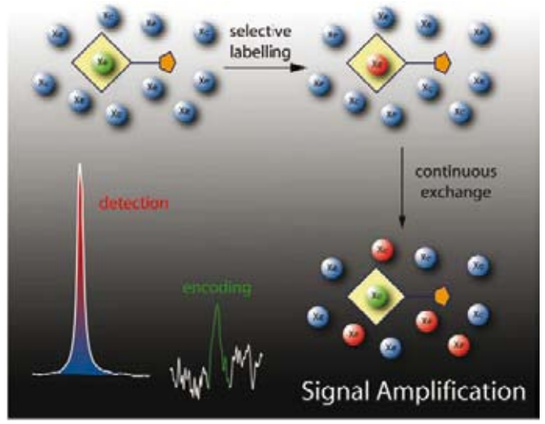

Figure 4: Signal amplification of the HYPER-CEST scheme is based on indirect detection of the biosensor information. Instead of direct detection of the noisy biosensor signal, the nuclei inside the molecular cage (green) are labelled with a radiofrequency pulse that erases their signal contribution. Continuous exchange accumulates these labelled nuclei and causes a significant decrease of the xenon signal from outside the cage that can be detected at much higher signal-to-noise (blue). Storing the information from the biosensor (red) in this signal yields a huge sensitivity gain.

difference between these two MRI datasets yields an image where signal remains only where biosensor is present. HYPER-CEST was demonstrated to boost the sensitivity of xenon biosensor MI by 10,000 times, making signal averaging unnecessary and reducing the acquisition time for mapping spatial distribution of a protein at micromolar concentrations (Figure 5) by several orders of magnitude [8].

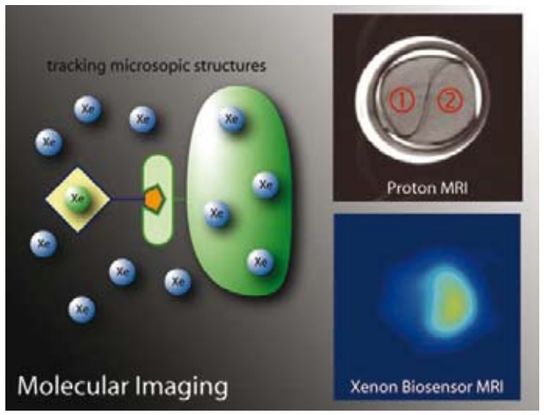

Figure 5: Microscopic structures that are labelled with avidin can be targeted with a biotinylated biosensor. In this example, the sensor is only present in compartment 2. The HYPER-CEST technique allows fast acquisition of molecular images with near-zero background.

Applications from cell tracking to biomedical imaging:

Feasibility studies on perfusion phantoms illustrate a very promising prognosis for future applications with biomedical interest. Possible limitations in terms of different relaxation behaviour or exchange dynamics in cell suspensions or under *in vivo* conditions should be compensated by optimized polarizers and the improved xenon biosensor exchange dynamics at body temperature. Cell tracking for *in vitro* experiments will be the next step in xenon MI, using the next generation of optimized biosensors (Figure 6) allowing to push the detection limit down to the nanomolar range. Implementation of the ultra-sensitive HYPER-CEST detection is possible for any MRI sequence that maps the distribution of xenon dissolved in tissue. Hence, there are no special requirements for the MR scanner, except for a broadband transmitter/receiver unit. Polarizers that produce large amounts of hyperpolarized ^{129}Xe are already commercially available [9]. Application of HYPER-CEST in a clinical setting would likely involve administering a targeted biosensor (e.g. an atherosclerosis marker [10]) to a patient, obtaining conventional ^{1}H MRI reference images, then delivering polarized xenon gas via inhalation and immediately acquiring the molecular image of vulnerable plaques using HYPER-CEST. Ultimately, addition of HYPER-CEST to the MRI toolbox would enable a MRI-based comprehensive radiological examination [11]. Although xenon biosensor imaging may still be years away from clinical use, xenon lung and tissue imaging is currently in Phase II clinical trials and will pave the way for future sophisticated applications of the noble gas.

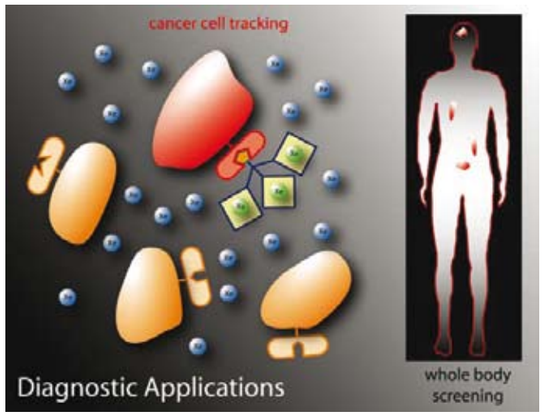

Figure 6: Potential applications of xenon biosensor MRI range from in vitro cell tracking to whole body screening in cancer diagnostic. The next sensor generation will be more sensitive due to "chemical amplification", using several molecular cages per sensor to encode the xenon signal.

Leif Schröder, Thomas J. Lowery, Christian Hilty

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The Belgian Museum of Radiology

The Belgian Museum for Radiology has been open to the public since 1990 and along with the museum at Remscheid-Lennep in Germany and the museum of Palermo in Italy make up the three radiology collections.

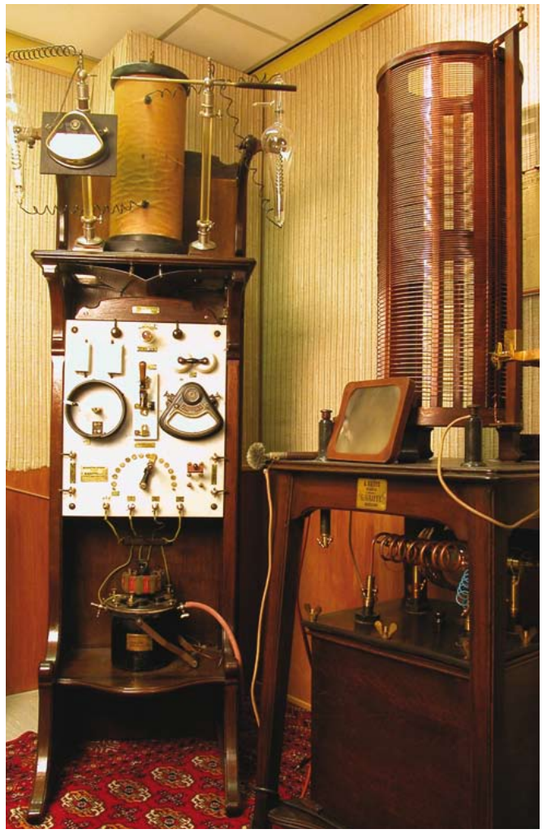

Figure 1: This widely-distributed "Art-Nouveau" model, elaborated by A-J. D'Arsonval, (France, 1851–1940) and manufactured by G Gaiffe (France 1857–1943) enjoyed an excellent reputation and over the years underwent a number of improvements. Here, it is shown with the famous Rochefort high voltage coil at the top of the device supplied by alternating current through a mercury and gas atmosphere turbine at the bottom.

A Belgian military radiologist, who was interested in the early years of the discovery of X-rays and the evolution of its technology, decided with a small team of volunteers in around 1980 to set up a museum devoted to radiology to commemorate the centennial of the discovery of the X-rays in 1895 by Röntgen.

The museum is housed in the radiology department of the military hospital Queen Astrid. While waiting for their examinations the patients may read educational posters in the hallways, which will enable them to learn about the progress of this specialty and obtain relevant information about the different applications of the X-rays in medicine. The museum is also open to the public interested in the evolution of the technologies that are applied to medical imaging, such as conventional radiology, ultrasound, digital radiology, computer tomography and magnetic imaging.

The educational posters teach the reader about the application of radiology in other domains other than the medical field, which include the arts, Egyptology, philately and industry. The museum displays reconstructions of radiology rooms. The laboratory of Professor Röntgen (1895) sits next to the radiology room of Dr Henrard (1919), who was a Belgian pioneer and founding member of the Belgian Journal of Radiology.

Next one finds a radiology room from the inter-war years, a radiology field set dropped by parachute in Bastogne in December 1944, or a neuroradiology room as it was equipped during the golden years of the 1960s.

The first scanner in Belgium - the second to be built worldwide - was set up in the department of Professor Collard in Charleroi. A further room is devoted to ultrasound. In a classroom, which is especially designed to welcome visitors, various films are shown. The first one called "The X past recomposed" is unique in the world. It follows the prolegomena of the discovery of X-rays. The second one "From Röntgen to the Euro tunnel" shows the birth and growth of the technology of radiology in Belgium. The museum also has a website, and has released several publications, comic strips, slides, a video and a CD-rom.

Dr Rene Van Tiggelen
Curator/conservateur
Belgian Museum for Radiology

For more information on the Belgian Museum of Radiology E-mail: info@radiology-museum.be or visit the website: www.radiology-museum.be.