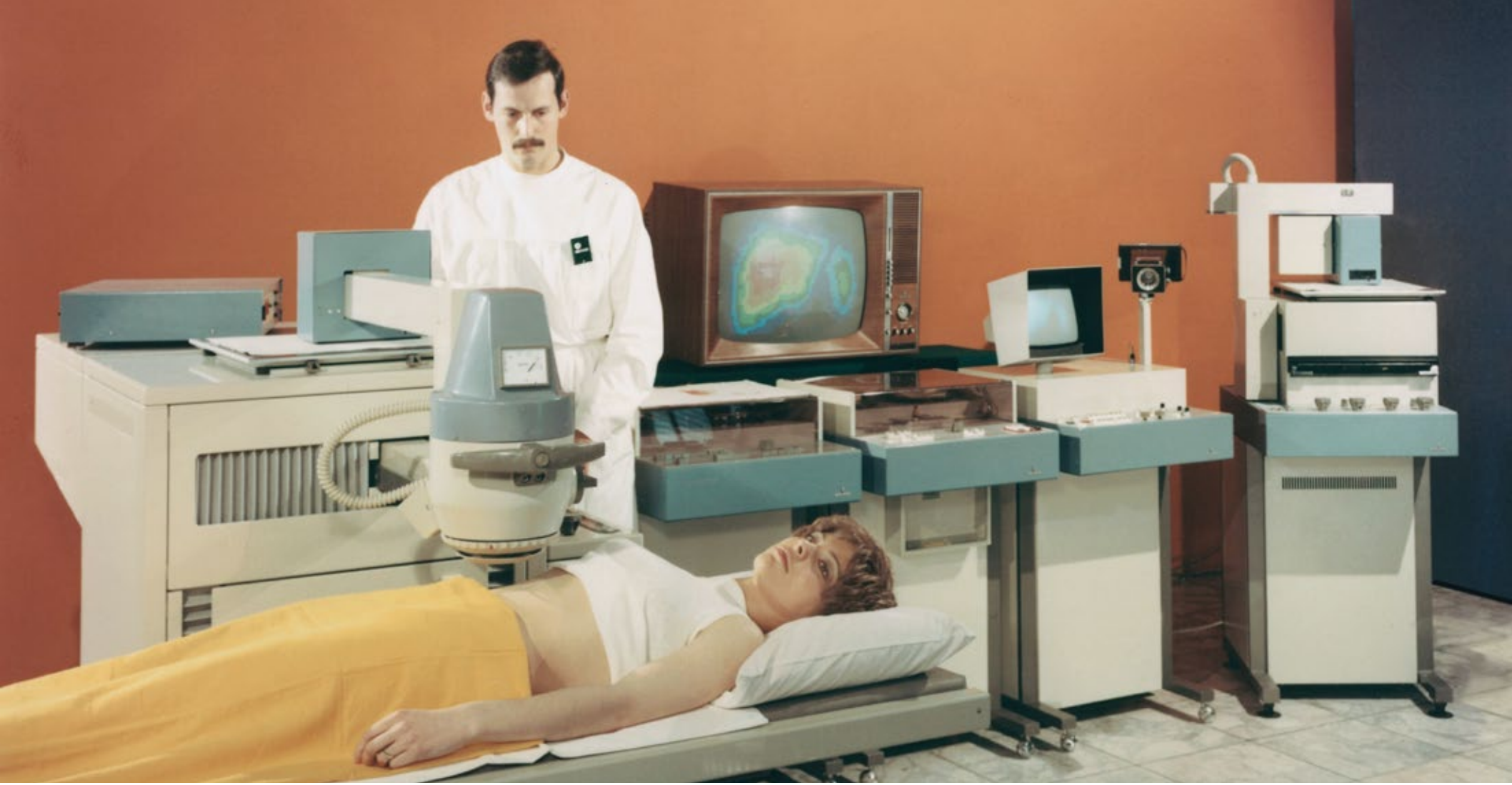

Siemens Healthineers Historical Institute

The History of Nuclear Medicine and Molecular Imaging at Siemens Healthineers

SIEMENS Healthineers

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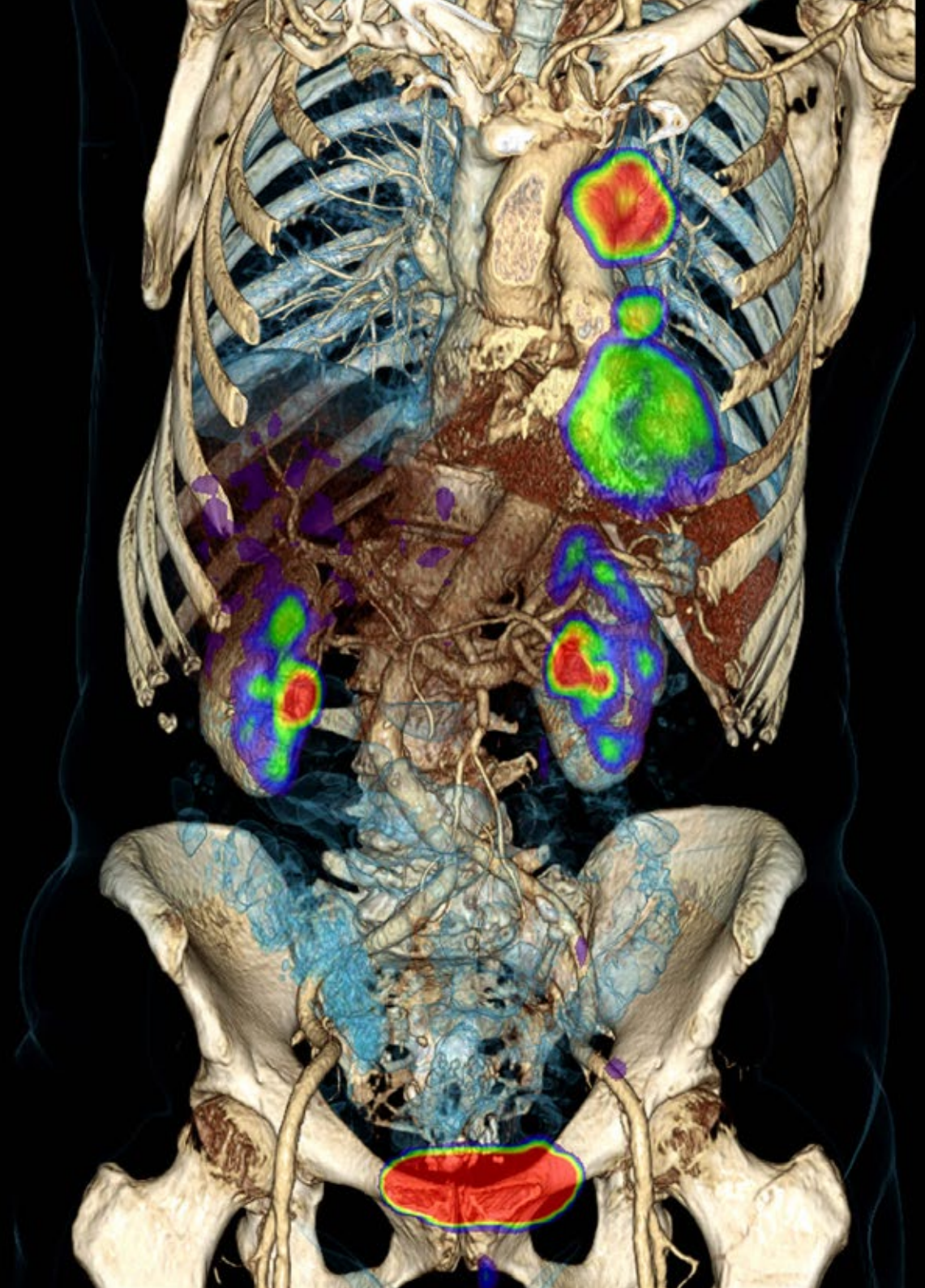
The History of Nuclear Medicine and Molecular Imaging at Siemens Healthineers

Content



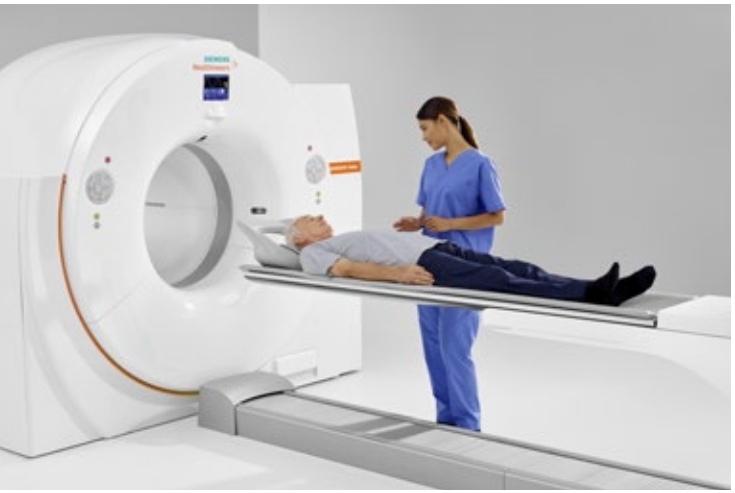
Participating tracers

How physicians watch their patients' metabolic processes on a monitor

Sometimes the stories behind important technologies begin with a pioneering discovery, an idea, or a flash of genius on the part of an individual researcher. When Wilhelm Conrad Röntgen discovered X-rays in 1895, he single-handedly helped revolutionize the world of medicine. However, the history of nuclear medicine cannot be traced back to a *single* event that immediately demonstrated its potential applications in medicine. Rather, it took decades for the underlying physical principles to be established and for development of the technology to yield clinical applications. Over the years, this process involved more prominent researchers and future Nobel laureates than virtually any other specialized field, including Henri Becquerel, the Curie family, Ernest Rutherford, Niels Bohr, George de Hevesy, and Robert Hofstadter – with Wilhelm Conrad Röntgen also playing a significant role.

The extraordinary history of nuclear medicine is matched only by its extraordinary underlying principle: a physician administers a weakly radioactive substance to the patient in order to treat a disease or to visualize bodily functions such as metabolic functions. The latter – diagnostics achieved with nuclear medical equipment – goes by the technical name of *molecular imaging*. In terms of its methodology and technology, it is fundamentally different from the other medical diagnostic procedures. With X-ray based diagnostics, the radiation source is located inside an X-ray tube and the X-ray apparatus "shines through" the patient. In molecular imaging, the patients themselves are the source of the radiation. The substance administered to the patient before the scan is for example a type of weakly radiolabeled glucose, known as a tracer. The tracer participates in the metabolic processes of the body – without having influence on them – and emits tiny doses of radiation over the course of a few hours. This radiation is measured by the highly sensitive systems used in nuclear medicine, which use it to generate images of the internal functions of the body.

Modern medical imaging procedures each have their own particular strengths. Broadly speaking, these can be broken down as follows: conventional X-ray provides a straightforward way of producing meaningful images; computed tomography (CT) delivers three-dimensional X-ray images in very high resolution and can therefore visualize extremely small vessels, such as those on the heart muscle or in the brain; ultrasound systems can produce detailed moving images of almost any type of bodily tissue; and magnetic resonance imaging (MRI) depicts soft tissue in unrivaled contrast. These technologies primarily help the physician examine the body's anatomy in great detail and identify any changes.



The strength of molecular imaging, however, lies in functional diagnostics. Physicians can observe metabolic processes in their patients' organs on a monitor in order to investigate the cause of diseases. Depending on the medical problem, this involves one of three established molecular imaging procedures, each of which has its own strengths: classical scintigraphy for two-dimensional images of organs such as the thyroid; single-photon emission computed tomography (SPECT) for examinations of the heart or brain, for example; and positron emission tomography (PET), with its in comparison to SPECT superior resolution, for tumor diagnostics.

SPECT and PET generate three-dimensional, cross-sectional images that can depict the patient's metabolic processes from head to toe. They visualize bodily functions accurately but anatomy much less detailed than the other imaging techniques described above. These techniques however can be correlated and combined with SPECT or PET in order to unite the best from both worlds. In the early years of PET, physicians spent considerable time sitting in front of screens and comparing nuclear medical images with a patient's CT scans to correlate anatomy and biological function of a metastasis.

Today this is done with hybrid systems that super-impose images of metabolic processes onto those of anatomy to create what are known as fusion images. Possible combinations include CT with SPECT or PET and magnetic resonance imaging with PET, which was considered practically impossible until Siemens Healthineers introduced Biograph mMR™.

This book looks at the history of this "impossible" development of nuclear medicine along with numerous other discoveries and inventions. Its scope are the innovative contributions that Siemens Healthineers has made to advancing this technology and broadening its diagnostic capabilities. The emergence of what we now call nuclear medicine and molecular imaging took some unusual twists and turns, including the story of a chemist who, about 100 years ago, labeled his meat stew with radioactive substances in order to catch his landlady red-handed, an act which practically invented the principle of tracers. Before embarking on this colorful history, we begin by looking at the tracers and technologies of the present day. How do scintigraphy, SPECT, PET, and the hybrid systems of modern molecular imaging work?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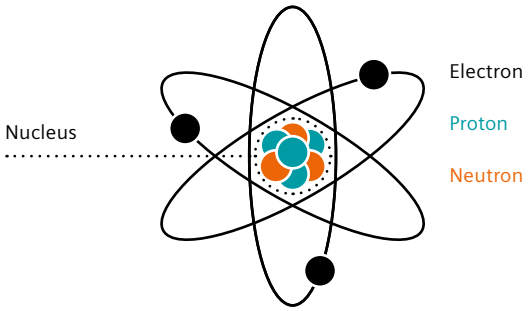
Molecular insights into the body

How radioactive substances facilitate disease diagnosis

What is radioactivity and how can it be put to specific use?

Radioactivity is produced by changes in the nucleus of an atom. Exactly how the particles in the nucleus behave in this process is best explained by reference to the Bohr model: everything in our world – whether it is a solid, a liquid, or a gas – is made up of atoms, which are made up of even smaller particles known as protons, neutrons, and electrons. The protons and neutrons are located in the nucleus, while the electrons orbit the nucleus in the electron shell. Depending on the type of atom, the nucleus is between 10,000 and 100,000 times smaller than the electron shell, yet it contains almost the entire mass of the atom. In the element helium, the nucleus contains normally two protons and two neutrons that are orbited by two electrons, whereas normal carbon contains six of each of these elementary particles. In general terms, nuclide simply means "type of atom".



Nuclides with the same number of protons or atomic number belong to the same element and are called isotopes, which can be differentiated by the number of neutrons in the nucleus.

All isotopes of an element have the same chemical properties, but the processes taking place inside the nucleus vary depending on the number of neutrons, and the nucleus can have a stable or unstable structure. Unstable nuclei have a tendency to stabilize themselves without outside influence. It is this restructuring process called radioactive decay that produces radioactivity, whereby the nucleus releases energy either as a stream of particles or in the form of electromagnetic waves.

Nuclear physics distinguishes between three types of radioactive decay and radiation: alpha, beta, and gamma radiation. Alpha decay produces new helium nuclei, which are emitted in the form of particles and travel for very short distances. Although the particles reach speeds of over 15,000 kilometers per second, a single sheet of paper is enough to stop them in their tracks. A radiation with a longer range is produced by beta decay, in which a neutron is converted to a proton or a proton to a neutron. During this conversion an electron or a positron (positively charged electron) is emitted from the nucleus as Beta or Beta plus radiation. The resulting stream of electrons can almost reach the speed of light and is able to penetrate tissue to a depth of several millimeters to centimeters. Nuclear medicine is especially interested in the third type of radioactivity, gamma radiation. This type of radiation is produced as a byproduct of decay in almost all nuclear transformations, with the excess energy emitted as electromagnetic wave. Like visible light, this radiation can be described also as individual photons (particles of light).

The 118 elements, or atomic species, in the periodic table of elements take the form of over 2,500 isotopes, around 250 of which are stable while all others spontaneously disintegrate. All unstable atomic species are radioactive and therefore referred to as radionuclides. The time it takes for half of the nuclei in a radioactive substance to decay is called the half-life: this figure is specific to each radionuclide and ranges from fractions of a second to billions of years. The half-life of the heavy metal Plutonium-239 (^{239}Pu) is around 24,000 years, whereas that of the weakly radioactive species Technetium-99m (^{99m}Tc) is around six hours; the latter is used in nuclear medicine examinations of the thyroid, for example. There is a close relationship between the half-life and the *Becquerel*, a physical unit indicating the number of decays in the atomic nucleus of a given radioactive source (activity), with one Becquerel corresponding to one radioactive disintegration per second.

The half-life can be used as a type of cosmic clock. For example, the age of planet Earth – around 4.55 billion years – was determined based on the time it takes for isotopes of uranium in rock to decay into lead. Similarly, a method known as radiocarbon dating can be used to work out the age of the remains of living creatures, such as Ötzi the Iceman. This method involves measuring the relative level of the isotope carbon-14, half of which decays in 5,730 years. Natural radioactivity is omnipresent in our environment and in our bodies: We are exposed to cosmic radiation, particularly in the mountains or on a plane. We inhale terrestrial radioactive isotopes originating from the Earth's crust; and we ingest radionuclides in our food and drinking water. One of the most frequent radioactive isotopes in our bodies is potassium-40, because all natural potassium always contains a fraction of K-40. Potassium is an essential mineral in the human being.

Lock and key – the principle behind tracers

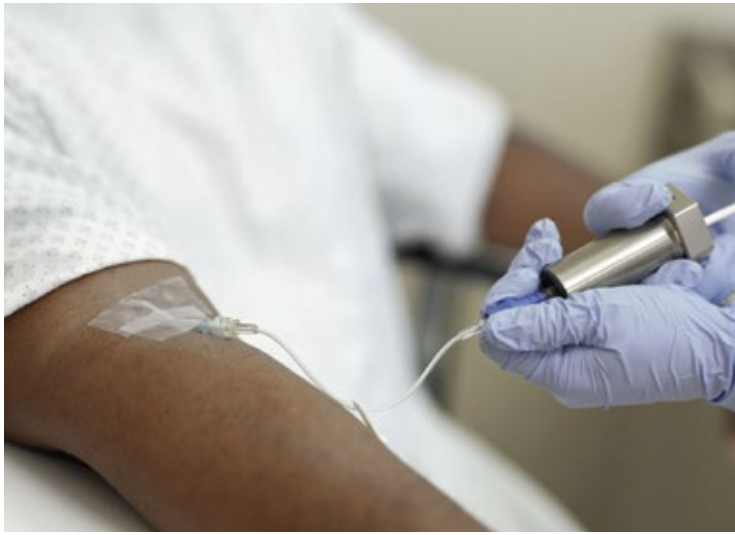
Nuclear medicine takes advantage of the characteristics of radioactivity, by using manufactured radioactive isotopes instead of natural radionuclides. These isotopes are used in chemical compounds called radiopharmaceuticals. This approach has a number of advantages as these isotopes have a short half-life, the radiopharmaceuticals do not affect the metabolism, and can be prepared for a specific medical purpose. Therapeutic radiopharmaceuticals are selected to deliver their effect almost exclusively in the target organ. As beta radiation can only travel a few millimeters within the body, it acts principally at the intended treatment site. Diagnostic radio-pharmaceuticals are selected by the physician for their special chemical properties, allowing the identification of the correct cells in the body according to the lock-and-key principle.

Thyroid scintigraphy, for example, uses a tracer with identical or very similar chemical properties to iodine. After the injection, it takes about 10 to 20 minutes for the tracer to accumulate in the thyroid. Cells with increased metabolic activity, such as hot nodules, take up larger quantities of tracer than normal tissue. By measuring the gamma radiation emitted by the tracer, a scintigraphy system generates images known as scintigrams, in which tissue with increased metabolic activity is shown in a range of colors. Among other things, these allow functional disturbances to be identified even before changes appear in the tissue.

Nuclear medicine uses artificial tracers that decay very quickly into non-radioactive elements. For example, in SPECT, the frequently used isotope Technetium-99m (^{99m}Tc) has a half-life of just six hours. Thanks to modern technologies and tracers, the radiation dose received in today's scintigraphy procedures roughly corresponds to that of a conventional X-ray. For a PET scan, the radiation dose is comparable to going on a two-week skiing vacation in the mountains. Allergic reactions to tracers are extremely rare, and patients are also fully fit to drive after a scan.

What does a nuclear medicine examination involve?

Almost all nuclear medicine examinations can be performed as an outpatient procedure. After patient history and informed consent, a tracer – e.g. radiolabeled glucose – is injected into a vein. Frequently the patient has to wait until the tracer reaches the target organ. How long this takes differs according to the type of examination, usually around fifteen minutes for thyroid scintigraphy, around an hour for a heart scan, and up to three hours for bone



scintigraphy. The actual scan usually lasts 5 to 40 minutes. One or two gamma cameras are positioned as close to the body as possible or rotate around the body while the patient lies on the examination table. In an examination with one of the modern hybrid systems, SPECT/CT, PET/CT, or PET/MR, the patient lies on an examination table while the table moves into the ring-shaped opening of the scanner. The systems scan the body step by step and convert the measurements into three-dimensional images.

The scan is completely painless, side effects are extremely rare, and the patient can immediately drive or go to work afterward. Drinking fluids helps eliminate the tracer as the body excretes the substance via the kidneys. Most of the radiation vanishes a few hours after the examination. In principle, there is nothing to rule out the use of molecular imaging in breastfeeding mothers and pregnant women, but scans should be reserved for urgent, exceptional cases.

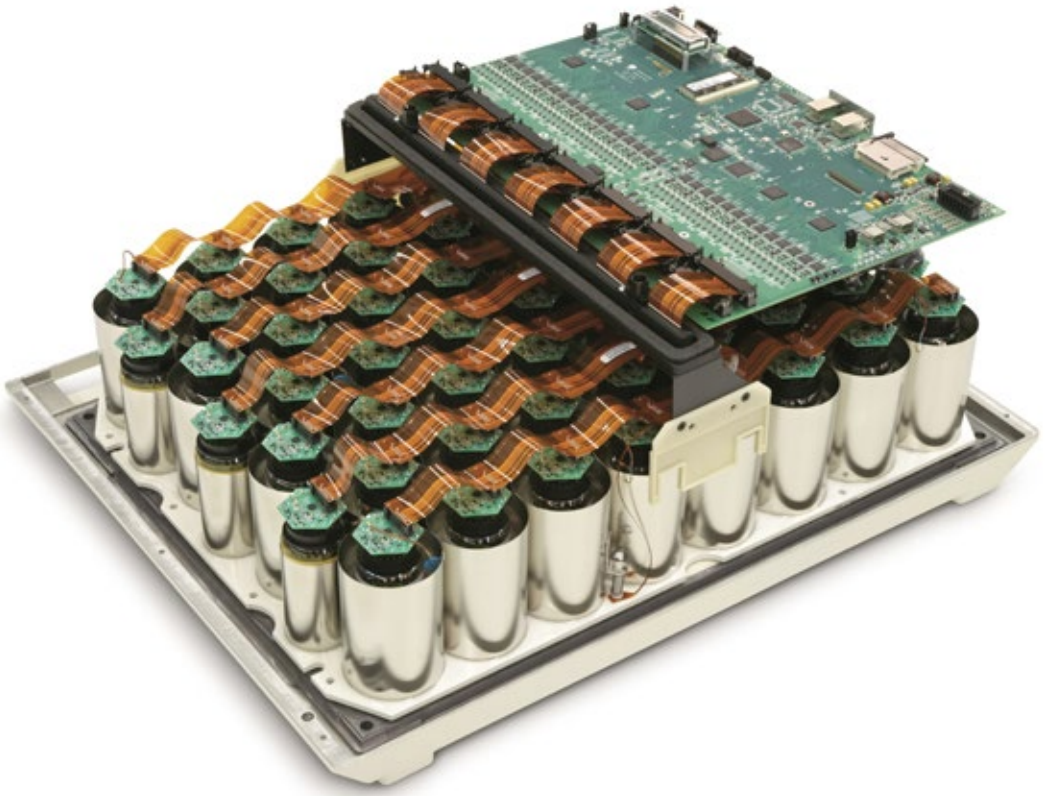
Crystals and flashes of light

The technology behind conventional scintigraphy and its benefits

Conventional scintigraphy provides a quick method of visualizing a patient's metabolic processes. It is often referred to as planar scintigraphy because, like conventional X-ray, it produces *flat* (planar), two-dimensional images. Scintigraphy can be used in virtually all organ scans, including suspected cases of hyperthyroidism, inflammation of the skeletal system, or kidney dysfunction.

The heart of a modern scintigraphy system is the gamma camera. It contains a number of wide measuring heads that convert gamma rays, emitted by the injected tracer, into electrical signals. Inside each measuring head, the gamma rays first collide with crystals, where they produce scintillations (flashes of light, from the Latin *scintilla*, "spark"). Photodiodes or photomultipliers then convert this light into electrical signals, which are used to generate the image. The general principle behind image creation is that the more rays the camera detects at a given location, the more flashes of light and electrical signals are produced. The number of electrical signals is used to generate the image information. In simple terms, the image content is created from the number of electrical signals at a given location.

To a large extent, the image quality of a gamma camera depends on what is known as the collimator. A collimator is an aperture made of lead and has a similar task like a lens for a camera. Only radiation arriving at the gamma camera from a certain angle is allowed in by the collimator. Scattered radiation, which could result in a blurry or even distorted image, is blocked out. The quality and construction of the collimator have a considerable influence on the sensitivity of the gamma camera, which in turn affects the required radiation dose: the more sensitive the measuring system, the lower the dose for the patient.




Symbia

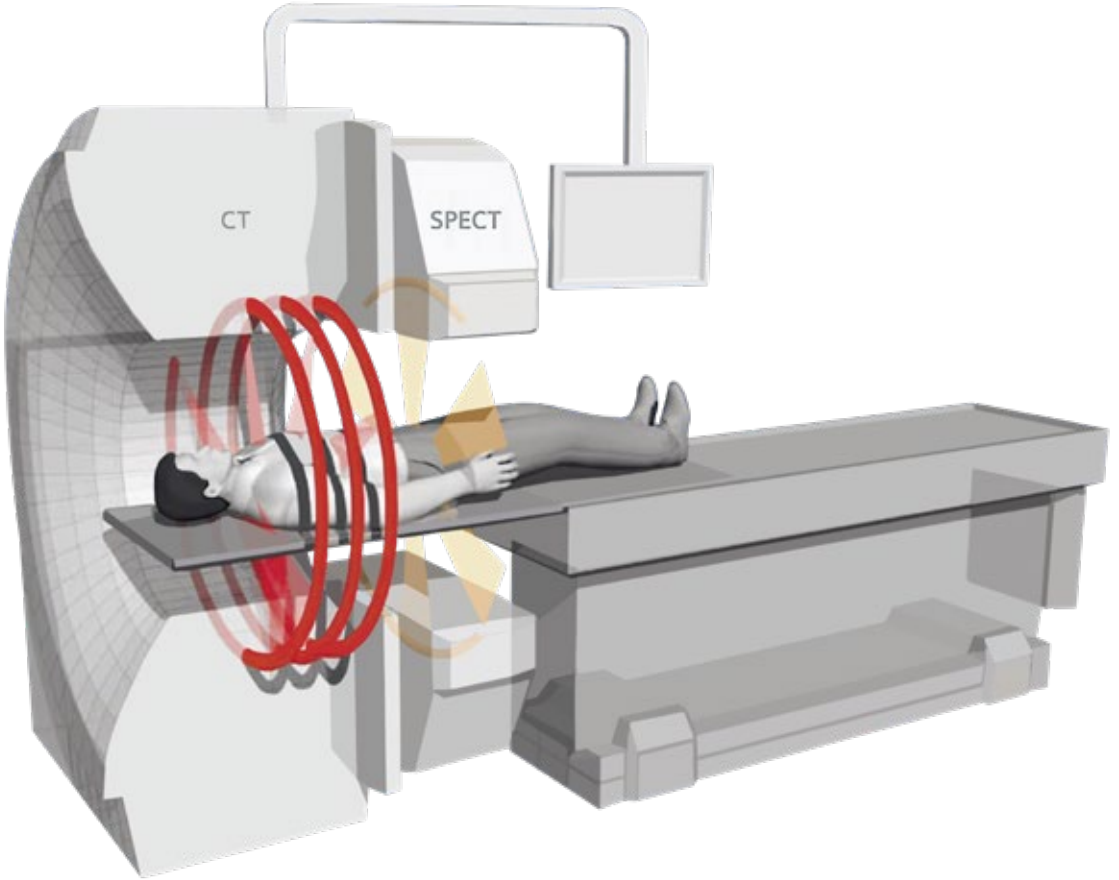
The third dimension

How do SPECT and SPECT/CT work?

Single-photon emission computed tomography (SPECT) is based on the same technical principle as conventional scintigraphy and uses scintillation crystals to capture the distribution of the tracer. With SPECT, two gamma cameras rotate around the patient in order to take pictures from various angles. The system uses the individual images to generate tomograms (cross-sectional images) that depict metabolic activity in three dimensions.

Tomograms are free of superimposition: unlike two-dimensional images, bodily structures in the foreground do not affect the depiction of those behind them. The physician can view metabolic activity as if individual thin slices were extracted from the body. The three-dimensional representation means that the location and extent of metabolic processes is clearer in SPECT images than in planar scintigrams. However, SPECT also only shows an outline of the anatomy. For this reason, many medical problems are investigated using systems that combine SPECT with computed tomography (CT) as CT can visualize anatomical details on a submillimeter level.

A hybrid SPECT/CT scanner also houses the CT components. An X-ray tube and a detector on the opposite side revolve around the patient several times a second and "shine through" them from all directions. The tomograms that the CT scanner generates from these images are subsequently fused with those from the SPECT scanner. In assessing a heart attack, for example, the images allow physicians to see quickly and accurately which coronary vessels are narrowed or occluded by coronary artery disease.

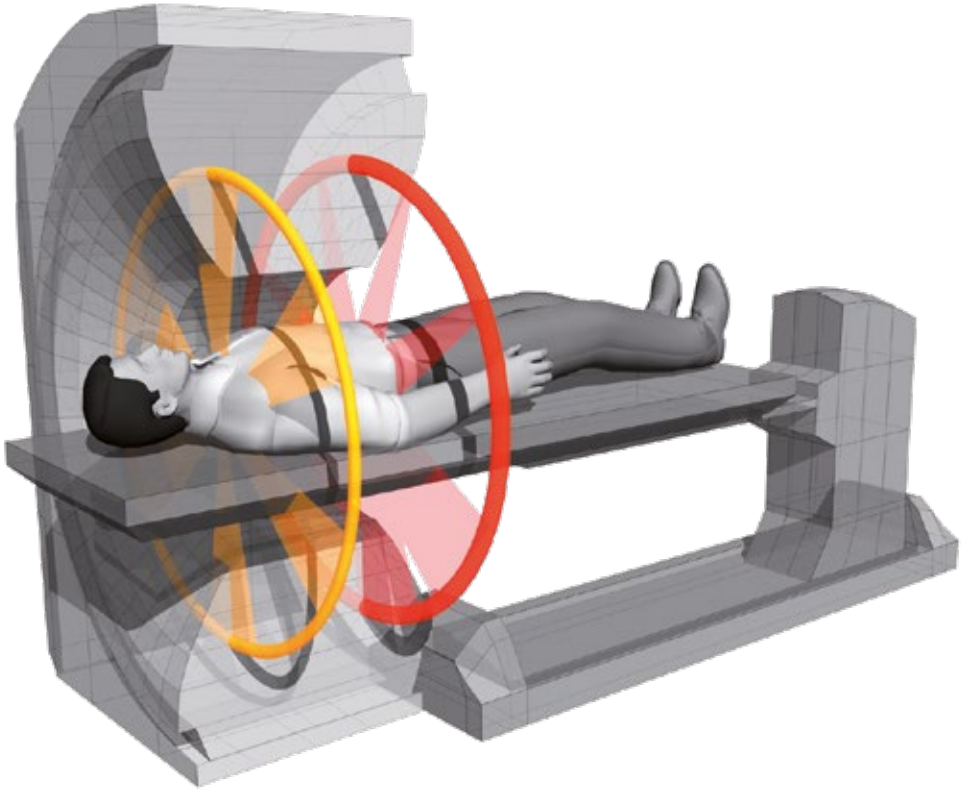


Positive annihilation

The strengths of PET and its hybrids

Although it is also based on the use of tracers and scintillation, positron emission tomography (PET) takes advantage of other characteristics within nuclear physics such as the decay of a proton-rich atomic nucleus that produces positrons. The positron, which has a positive electrical charge, is the anti-particle of the negatively charged electron. If a positron collides with an electron after a nuclear decay, the two particles annihilate one another. This produces two photons that move away from each other at the same speed and approximately an angle of 180°. The detection of both photons therefore allows the scanner to locate the annihilation event with great precision.

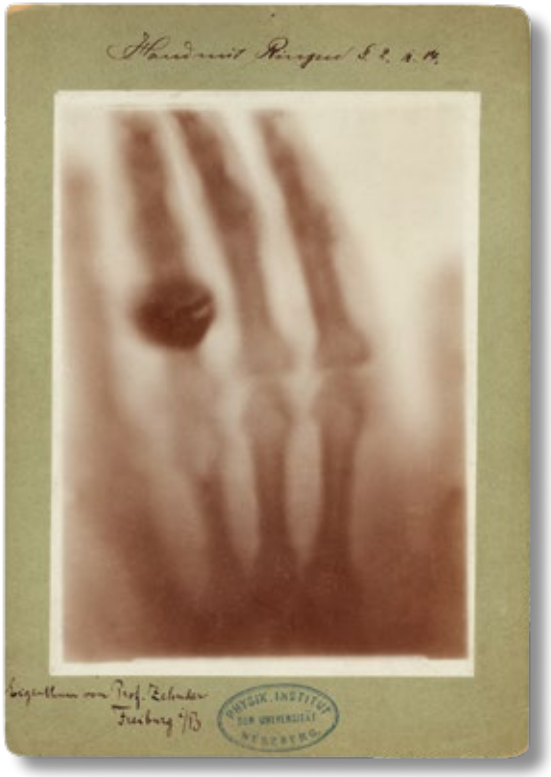
In a PET scanner, the scintillation crystals are arranged in a ring inside the gantry. When the two emitted photons collide with two crystals on opposite sides at specific times, they create a mathematical line of response. The system computer can use this to calculate, with a high degree of accuracy, where and when the positron and electron annihilated one another. Based on a large number of these reactions, the computer generates a color slice image. This technique is able to map the distribution of tracer in the body more precisely than SPECT, but the tracer requires considerably more effort to prepare. The tracer typically used in PET is the radioactive sugar fluorine-18 deoxyglucose, which has a very short half-life of just under two hours.



PET is primarily used for tumor diagnostics, examinations of the coronary vessels, and assessment for disorders of the nervous system. Today, the resulting three-dimensional images of metabolic processes are almost always superimposed onto anatomical images of the body. Although it is possible to combine images from separate systems, via software fusion, the result is less accurate than the fusion images from hybrid systems that combine positron emission tomography with computed tomography (PET/CT) or with magnetic resonance imaging (PET/MR). Examinations with PET in isolation are very rare nowadays.

“This is magic!”

The history of radioactivity and the early days of nuclear medicine



Bertha Röntgen’s hand

Nuclear medicine began in the late 19th century during one of the most exciting chapters in the history of the natural sciences. In the space of just a few decades, technology had radically transformed people’s everyday lives. The first motorized streetcars were operating in cities, the streets and alleyways were lit with electric lamps, and people were using elevators, sending telegrams, and having their photos taken. All of these inventions were the result of empirical knowledge acquired by engineers over a lengthy process of trial and improvement. The technologies worked, but no one at that time was sure exactly how or why. The structure of the atom remained an impenetrable enigma. Why did certain elements react with one another to form chemical compounds? What forces were at play within matter itself, and what was its structure? Was matter actually made up of indivisible atoms? Answers to these questions would emerge later, following two of the most important discoveries in the history of science: X-rays and radioactivity.

“Röntgen must have gone mad”

In the late 19th century, physics laboratories all over the world were focusing on electrodynamics, the theory of electricity and magnetism. As well as experimenting with coils and generators, scientists began generating magnetic fields and observing gas discharges in almost completely evacuated tubes. On November 8, 1895, one such vacuum tube was standing in a laboratory in the Institute of Physics at the University of Würzburg. When the physicist Wilhelm Conrad Röntgen began his experiments with the room completely blacked out, he noticed a bright glow emanating from the corner of his laboratory, where there was a screen coated with a phosphorescent substance. This light could not have come from the tiny gas residues inside the glass tube, as Röntgen had wrapped the tube in black paper and it followed that the tube must be emitting an unknown, invisible form of radiation. Röntgen placed a thick book between the tube and the screen, but the rays simply passed straight through it. He then held his hand in the path of the mysterious emissions and made what was probably the most exciting discovery of his lifetime: on the screen, he could clearly make out the shadows of the bones in his hand.

Initially, Röntgen kept his discovery to himself and allowed no one to enter his laboratory. “I didn’t talk about my work to anyone; I told my wife that when people heard what I was doing they would say, ‘Röntgen must have gone mad.’” Around seven weeks later, Röntgen was ready to publish his discovery and wrote a paper entitled *On a New Kind of Rays*. He wanted to include a few photos as evidence, so he asked his wife, Bertha, to place her hand on a photographic plate. By “radiographing” her hand with X-rays for fifteen minutes, he ended up taking one of the most famous photos in the world. It showed the bones of Bertha Röntgen’s hand with a ring that

Wilhelm Conrad Röntgen,
photo taken in 1900

appeared to be floating around one of her fingers. Soon after the article was published on January 1, 1896, "all hell broke loose" as Röntgen predicted. News of the sensational discovery spread around the globe in just a few days, captivating scientists and the general public alike. In the ensuing "X-ray fever" people began X-raying everything including purses, doors, furniture, and the human body. The French physicist Henri Becquerel was fascinated when he heard about X-rays in greater detail at the French Academy of Sciences in Paris on January 20, 1896. Resolving to apply the new findings to his own research, Becquerel got to work immediately.

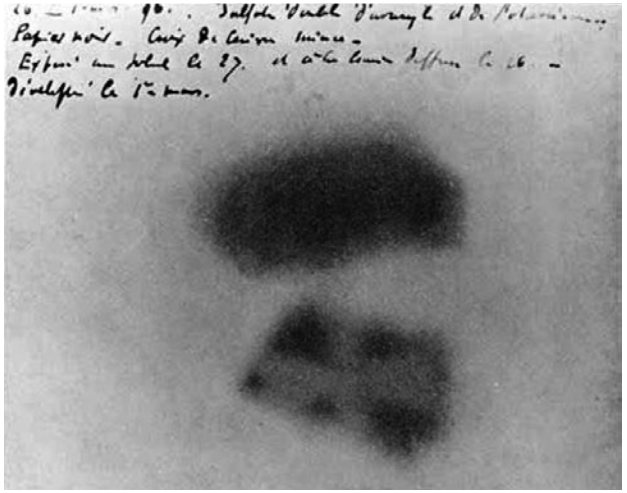
Uranium in the drawer

Becquerel suspected that X-rays were physically related to the phenomenon of fluorescence, which causes certain substances to glow when energized. His first experiments were very straightforward. Becquerel began by placing a lump of uranium salt on a photographic plate and then left it out in the sun for a few hours. When he developed the photographic plate the next day, he could make out the blurry outlines of the salt. He planned to repeat the experiment in the last week of February 1896, but cloudy skies over Paris thwarted his attempt. Becquerel left his prepared experiment, the uranium salt and the photographic plate, in a drawer. After retrieving it on March 1, 1896, he developed the plate and was astonished to find that the outline

Becquerel in his lab

was much clearer than in the experiments with solar radiation. The emissions could not, therefore, be due to fluorescence in the uranium. Becquerel immediately came to the correct conclusion that the uranium atoms emitted their own form of radiation, which was very similar to X-rays, produced by unknown processes in their interior.

This was a sensational discovery because, up until that point, physicists were certain that matter could not emit energy without first passing into an excited state. Strangely, Becquerel's rays failed to cause much of a stir. Physicists at the time were busy studying other recently discovered rays, such as the electromagnetic waves first demonstrated by Heinrich Hertz in 1886. The reasons behind the lack of interest were ultimately practical in nature: with Röntgen's discovery, it was clear from the outset that X-rays would revolutionize the world of medicine, whereas no one initially knew what to do with Becquerel's rays. This would remain the case until two years later when a young physicist in Paris began looking for a topic to guide her doctoral thesis.

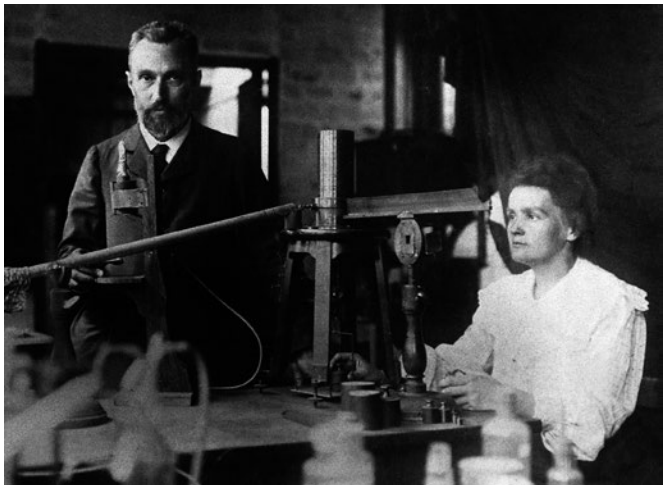


One of Becquerel's photographic plates

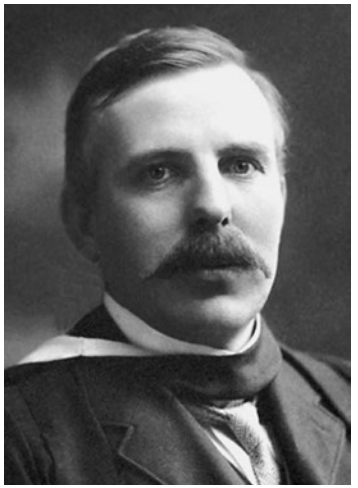
The Curies and the diabolical measuring device

Like many scientists in 1897, Marie Curie was fascinated by Röntgen's discovery of X-rays, and she toyed with the idea of writing her thesis on X-rays. However, her husband Pierre advised her to study the hitherto-neglected Becquerel rays. Pierre Curie was familiar with the basic features of Becquerel's work, and Becquerel previously conducted experiments using an electrometer developed by Pierre and his brother, Jacques. This device could be used to measure small currents but like a number of other scientists, Becquerel had problems with the extremely sensitive and complicated instrument. (A few years later, the physicist Lord Rayleigh would write in his notes that all electrometers were "designed by the devil.") Pierre organized a small room on the ground floor of the City of Paris Industrial Physics and Chemistry Higher Educational Institution, where he improved the electrometer and spent 20 days helping Marie familiarize herself with the device. The instrument was now so precise that Marie was able to measure changes in the conductivity of air caused by Becquerel rays.

Marie began her experiments in 1898 and the work she did over subsequent years was some of the most impressive and momentous in the history of science. She conducted all kinds of extraordinary experiments that led to sensational new insights, and almost all her work centered around the phenomenon she christened "radioactivity". In some areas of her research, Marie required a lot of dexterity, whereas others called for physical stamina and a strong pair of arms. In her experiments relating to Becquerel rays, she used basic equipment, such as glue, wire, tin, and glass, to study a variety of salts, metals, and minerals. She once managed to analyze thirteen elements in a single day and, in the process, she made the simple but important observation that radioactivity can be measured. This observation could then be applied to the search for new elements.



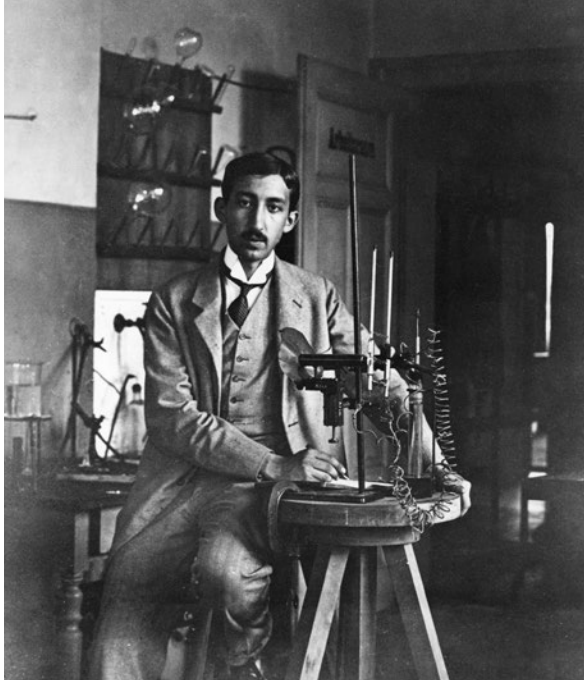
Marie and Pierre Curie, around 1900



Nobel photo of Ernest Rutherford, 1909

Some of Marie and Pierre Curie's most famous work relates to the discovery of two radioactive elements: polonium, which is named after Marie's home country of Poland, and radium, whose name is derived from the Latin *radius*, meaning "ray". In order for radium to be officially recognized as an element, the Curies needed to refine a sufficient quantity of it. Marie, who was stronger than her husband, set to work in an unheated garden shed, dragging, shoveling, and stirring huge quantities of pitchblende until she managed to isolate around 0.1 grams of radium from around one metric ton of the parent mineral. For her research into radioactivity, Marie received the 1903 Nobel Prize in Physics alongside her husband and Becquerel. In 1911, Marie was also awarded the Nobel Prize in Chemistry for achievements including the discovery and isolation of Radium.

All of this meant that the atom was not, as scientists previously thought, the smallest, indivisible building block of matter. What happens inside atoms during radioactive decay was first described by Paul Villard and Ernest Rutherford. Villard discovered gamma rays in his experiments with radium, while Rutherford demonstrated the existence of alpha and beta radiation, introduced the term "half-life", and received the 1908 Nobel Prize in Chemistry. Rutherford continued his research and formulated the Rutherford model of the atom with the nucleus at its center and the proton as a component of the atomic nucleus. Indeed, Rutherford's laboratory in Manchester was at the heart of some of the most significant discoveries in physics. Niels Bohr, who refined Rutherford's model of the atom, began his career there as a trainee, as did the man now considered the "father of nuclear medicine", George de Hevesy.



George de Hevesy as a student, around 1910

A magic stew

Manchester, fall 1911: George de Hevesy was a few months into his traineeship when Rutherford gave him a task that would shape the rest of his research career. Several hundred kilograms of pitchblende were stored in sacks in the basement of the laboratory. More precisely, the sacks contained radium-D and lead that were left over as decay products following the extraction of radium from pitchblende. Rutherford needed pure radium-D for his experiments and said to Hevesy, "my boy, if you are worth your salt, you will try to separate radium-D from all that lead." Of course, as we now know, Hevesy was doomed to fail because it is impossible to separate radium-D and lead since Radium-D is a lead isotope and therefore chemically identical to stable lead. However, this failure at least gave Hevesy an idea: he wanted to mark non-radioactive elements, such as lead, with radioactive elements, such as Radium-D, in order to use the latter as "tracers". He believed this principle would make it possible to measure chemical processes that previously eluded observation. Soon afterwards, a peculiar set of circumstances provided him with a perfect opportunity to test the basic idea of the tracer method.

It is no longer possible to say exactly how these events unfolded. Hevesy never recorded them himself, and the various biographies written about the scientist differ in the details. We know this anecdote actually took place because Hevesy gave a brief account of it at a conference, 50 years later: during his time in Manchester, Hevesy lived at a boarding house where the landlady served fresh meat on Sundays and goulash, mincemeat, or stew on other days. Hevesy began to suspect that she was reusing Sunday's leftover meat for the weekday meals. When he asked the landlady about it, she replied that the meat was cooked fresh every day. "One day, when she wasn't looking," Hevesy said at the conference, "I added a dose of radioactive material to the food." He borrowed an electrometer from the laboratory – and "the next day the hash was radioactive!" Several biographies record that the landlady exclaimed, "This is magic!" What they don't say is whether she served freshly cooked meat every day after that.

Following this episode, which probably took place in early 1912, Hevesy began conducting targeted research into the principle of tracers. Among other things, he used natural radionuclides and isotopes to study the chemical processes in plant, animal, and human tissue. He also determined the water content of the human body and measured the doubling time of tumor cells. Between 1912 and 1963, Hevesy produced some 400 scientific publications, including *Radioactive indicators. Their Application in Biochemistry, Animal Physiology, and Pathology*, which ran to 600 pages and went on to become the definitive work of early nuclear medicine. Hevesy's findings, and especially his work on the principle of tracers, paved the way for countless new observations, particularly in the fields of biochemistry and medicine. George de Hevesy was awarded the 1943 Nobel Prize in Chemistry, "for his work on the use of isotopes as tracers in the study of chemical processes."

The next family trip to Sweden

Marie Curie did not live to see her eldest daughter stand on the same podium she did 32 and 24 years earlier. The 1935 Nobel Prize, awarded to Irène Joliot-Curie and her husband Frédéric Joliot-Curie, was directly linked to the one awarded to her parents. Whereas Marie and Pierre had discovered natural radioactive elements, Irène and Frédéric demonstrated in 1933 that radionuclides could also be created artificially. Their experiments involved firing alpha particles at a piece of aluminum foil, which demonstrated alpha particles collide and merge with aluminum nuclei-produced phosphorus, which emits radiation for a short time before decaying into silicon. To verify the method, the Joliot-Curies bombarded other elements and produced other isotopes, such as radioactive aluminum from magnesium. The discovery was the next big sensation in atomic research and marked the first major step toward producing tracers optimized for medical applications.

Following the discovery of artificial radioactivity, research into medical applications gathered pace. Scientists converted chemical elements into new, previously unknown isotopes: some of these disintegrated in a fraction of a second, while others had half-lives running into the millions of years. The most commonly used tracer in nuclear medicine to date was created in 1938 from the artificial element technetium. Emilio Segrè and Glenn Seaborg

Irène and Frédéric Joliot-Curie
in their laboratory in 1935

generated technetium-99m, a radionuclide with a half-life of six hours. At around the same time, the physician Saul Hertz and the physicist Arthur Roberts recognized that isotopes of iodine were particularly well suited to thyroid examinations and could even help treat hyperthyroidism. The technical capabilities available to all of these pioneers were essentially based on two inventions: the Geiger-Müller counter and the cyclotron particle accelerator.

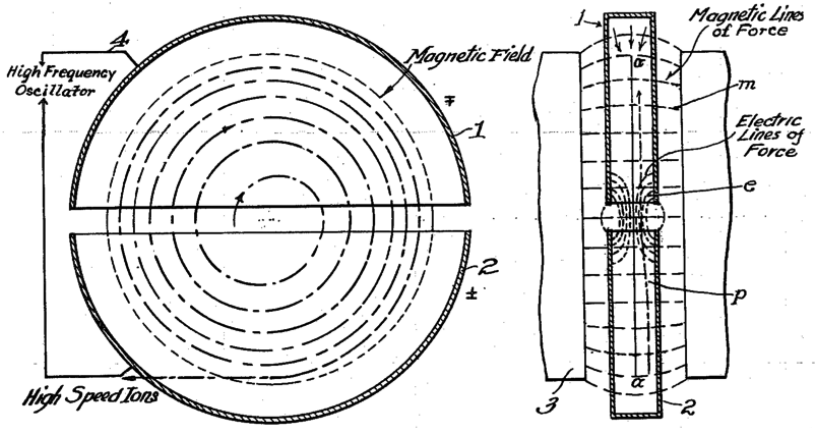
Laying the foundations for today's technology

Understanding and making intelligent use of the phenomenon of radioactivity was just one side of research into nuclear medicine. The other equally fundamental side centered around developing precise technologies that could create optimal tracers and measure their distribution in the body. As Irène and Frédéric Joliot-Curie discovered, the nuclei of some elements react with one another if you simply "fire" them at each other with low energies. In general, atoms or elementary particles need to collide at very high speeds in order to trigger nuclear reactions. In the 1920s, a number of physicists independently developed early ideas for particle accelerators that could accelerate electrically charged atoms (ions) to very high energies in a relatively small space using magnetic fields. Taking up these ideas in the early 1930s, Ernest O. Lawrence built a "circular accelerator," which he called the *cyclotron*. The apparatus generated a powerful magnetic field in order to accelerate particles within a circular vacuum chamber. Once the beam of particles had sufficient energy, a second magnetic field steered it toward a target. Lawrence refined the cyclotron over the course of several years, created his own artificial radionuclides for medical research, and went on to receive the 1939 Nobel Prize in Physics for this work. The principle of the cyclotron is still used in tracer production today, and the name is still used for this type of particle accelerator.

By the early 1940s, the technology for producing radioactive isotopes was astonishingly effective, but work on developing the corresponding detectors was still in its infancy. The first major milestone in the development of measuring technology was a device whose characteristic crackling sound is still recognizable today. Hans Geiger, who rose to international prominence as an assistant to Ernest Rutherford, developed a gas-filled tube in 1928 in collaboration with his doctoral student Walther Müller. When particles or rays hit the Geiger-Müller counter, the gas reacts and triggers electrical impulses that are then reproduced as a crackling sound on a loudspeaker. Strictly speaking, the commonly used colloquial term "Geiger counter" refers not to the entire instrument but only to the detector that counts the incident rays. The first practical measuring devices in nuclear medicine were based on the Geiger-Müller principle. However, the counter tubes were difficult to operate and required a great deal of dexterity as early nuclear medical practitioners had to cover their patients with grids or frames in order to make a rough estimate of a tracer's distribution in an organ. This method is not well suited for imaging.

Fifty years after the discovery of radioactivity, the era of modern molecular imaging was ushered in by three inventions that each built upon the last. The physicist Hartmut Kallmann realized that certain crystals absorb gamma rays and convert them into light. In order to measure the tiny flashes of light, Kallmann combined the crystals with a device known as a photomultiplier, which converts light into an electrical signal and amplifies it. By late 1946, the prototype of all modern scintillation counters was standing in Kallmann's laboratory. Two years later, the physicist and future Nobel laureate Robert Hofstadter improved the sensitivity of the scintillation

Ernest O. Lawrence, 1939



The principles of a cyclotron by Ernest O. Lawrence. Taken from US patent 1,948,384

counter by inserting atoms of sodium iodide into the crystal and thereby boosting its conductivity. Even today, many nuclear medicine instruments use sodium iodide crystals of this kind. The principle behind the third invention also provided the basis for further developments over the course of several decades and, in 1951, a group led by medical physicist Benedict Cassen built the first automatic scanner in the history of nuclear medicine. The device had a scintillation counter that measured the tracer's distribution while an electric motor moved it across the organ in a straight line. This scanning technique is the source of the technical term, rectilinear scanners.

Although all these devices were still relatively simple prototypes designed for scientific research, they had enormous potential for medical applications. It was at this stage that the first companies – such as the US-based manufacturer, Nuclear Chicago – became involved in efforts to refine the technologies. At Siemens the green light came on September 1, 1949, when Wolf Gellinek, head of development at the medical technology division, stated in a memorandum: "Siemens is interested in the further development of these indicator methods for tracking radioactive isotopes administered to humans and laboratory animals as so-called 'tracers.'" The history of nuclear medicine at Siemens Healthineers had begun.

Benedict Cassen (left) and the rectilinear scanner

Let there be light!

From the first scintigraphy apparatus to modern SPECT/CT scanners

By the mid-20th century, physicians already had an impressive number of technical tools at their disposal. X-ray units allowed them to visualize the lungs or even the ventricles of the heart; many laboratory analyses were already available; heart function and brainwaves could be measured electronically; and certain types of cancer could be treated using radiotherapy devices. However, many processes in the body remained invisible to the world of medicine. For instance, physicians could not see whether a patient's thyroid was producing too many hormones. Instead, they evaluated the metabolic process by feeling the organ and considering symptoms such as ravenous hunger and shaking. Yet the challenge remained that not every patient developed the same symptoms, and not every thyroid got bigger as a result of hyperfunction.

Theoretically, biological research in the 1920s demonstrated that the tracer method could deliver considerable improvements in the accuracy and reliability of diagnoses such as these. However, the method was still too rudimentary and, above all, too uncomfortable – for both doctor and patient – to be used in medicine. After World War II, the pioneers of nuclear medicine could generally be found tinkering away in basements, barracks, or former air-raid shelters. It was not until the early 1950s that the first "isotope departments", equipped with soldering irons, wrenches, and radiation meters with Geiger-Müller counter tubes, appeared at a number of hospitals. Pioneers working in therapy used radium or radioactive iodine, among other nuclides, in self-built diagnostic systems mounted on benches or metal frames.

Seeing without an image

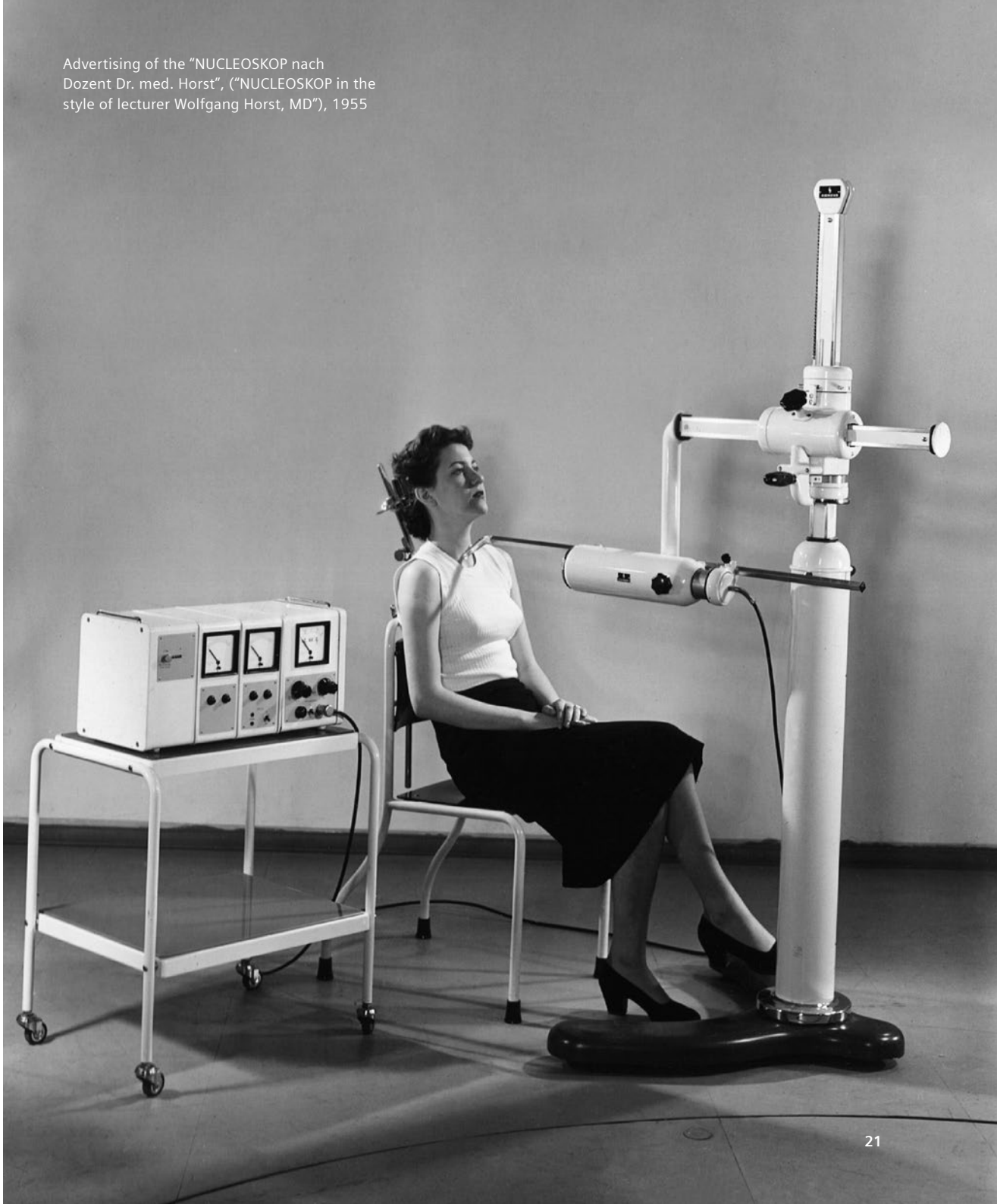
Meanwhile, at the headquarters of the Siemens medical technology division, in the Franconian town of Erlangen, work began, "on planning a scintillation measuring device for localizing iodine uptake in the thyroid." The five-year development period for the first nuclear medicine diagnostic unit from Siemens began with a search for techniques that could measure the distribution of iodine in the thyroid as accurately as possible. At the same time, it was important that the technology did not "impede efforts to minimize patients' exposure to radiation," according to an interim report by Siemens' scientific research division in 1953.

In those days, it was anybody's guess which approach would prove to be the most practicable. The Siemens engineers experimented with counter tubes that either moved across the patient's throat at various speeds or remained stationary. Some approaches were particularly well suited for measuring the size of the thyroid, while others delivered greater detail with respect to the distribution of iodine. Ultimately, the device that entered further development was a combination of several approaches: a lead-coated measuring head was held directly against the thyroid and could be fitted with a counter tube or scintillation crystal depending on the requirements of the examination. The lead sheath could be moved along the length of the measuring head, allowing operators to adjust how much of the organ they could "see." At this time, however, "seeing" meant something more like "reading," as the physician had to estimate the tracer distribution as accurately as possible using four dials on the apparatus.

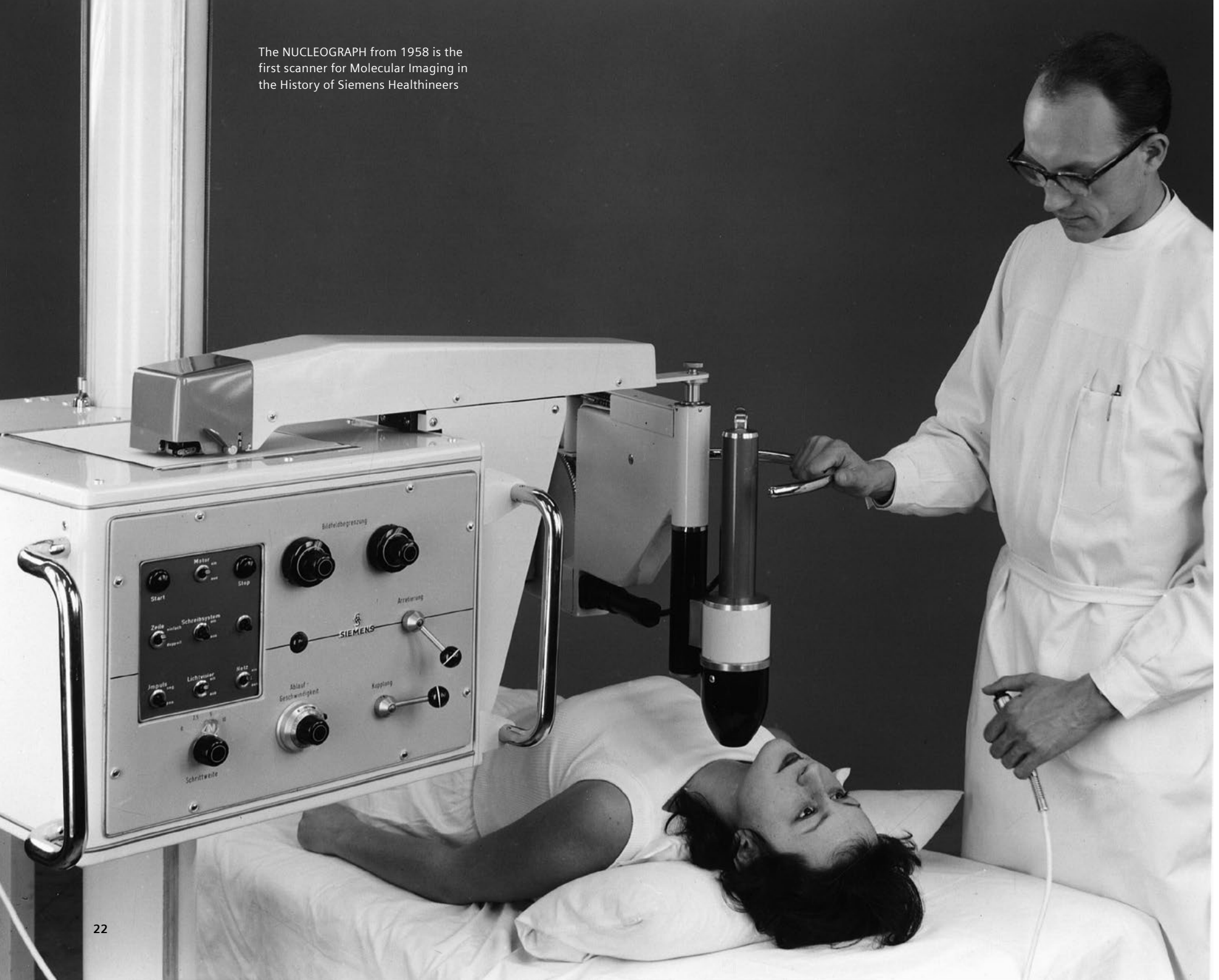
To optimize the device for practical use, researchers held numerous discussions with doctors and conducted tests at several hospitals. They worked closely with the radiologist Wolfgang Horst, who set up an isotope department at the University Medical Center Hamburg-Eppendorf (UKE) in the early 1950s. Minutes from Siemens' development meetings at that time refer to a number of major therapeutic achievements. For example, nuclear physicians in Hamburg used radioactive iodine to treat thyroid disorders. After treatment, 97 percent of the approximately 150 patients were symptom-free and no longer required thyroid surgery. The doctors in Hamburg wanted to use the Siemens measuring device to plan therapy more precisely and to monitor the development of the disorder.

Wolfgang Horst took part in several meetings at the Siemens research laboratory in Erlangen, offering his experience of practical applications and suggestions for the design of the apparatus. Among other things, it is recorded that, "Dr. Horst wanted a larger input window on the counter tubes," recommended dedicated tubes for examining children, and made proposals that influenced the construction of the stand. When Siemens launched the apparatus in 1955, it went by the illustrious name of *NUCLEOSKOP nach Dozent Dr. med. Horst* ("NUCLEOSKOP in the style of lecturer Wolfgang Horst, MD") in recognition of Horst's numerous suggestions, and in keeping with the ceremonious style of advertising in those days.

The NUCLEOSKOP was originally planned as a dedicated device for thyroid examinations because, during the design phase, these were seen as the only reliable application of nuclear medicine. During this phase, the Siemens engineers were working with physicians from University Hospital Erlangen on "special counter tubes," which could be used to measure metabolic processes in the liver, for example. Over the years, a steady stream of new applications were added to the list. The NUCLEOSKOP model from the year 1957 was suitable for all known tracers at the time and was used for therapy monitoring, to diagnose brain and liver tumors, and to measure tracers in the bone marrow, blood, and spleen.



Advertising of the "NUCLEOSKOP nach Dozent Dr. med. Horst", ("NUCLEOSKOP in the style of lecturer Wolfgang Horst, MD"), 1955



The NUCLEOGRAPH from 1958 is the first scanner for Molecular Imaging in the History of Siemens Healthineers

From the dial to the molecular image

By this time, Siemens accumulated 60 years of imaging experience and the company also produced devices for use in nuclear medicine at its Erlangen X-ray labs in the mid-1950s. When designing the first mass-produced nuclear medicine *scanner*, the engineers were able to draw from a number of existing imaging technologies, but they had to develop the "recording unit" from scratch. In simple terms, this unit was a radiation-measuring device connected to a printer. The electromechanical printing mechanism plotted the tracer distribution measured by the scintillation counter as a linear chart that represented the location of the metabolic process on a 1:1 scale. Known as a scintigram, this chart could be plotted on normal writing paper or on carbon paper to create up to four copies. Using very simple means, it was even possible to create what we now call as a fusion image: a scintigram was printed on tracing paper and overlaid on an X-ray to produce a true-to-scale representation of structures inside the patient's body.

Siemens called the new type of apparatus NUCLEOGRAPH and began manufacturing a small pilot series of five units in early 1958. By spring of that year, the NUCLEOGRAPH was already being used at a number of German hospitals, including at Wolfgang Horst's isotope department in Hamburg-Eppendorf. However, according to a Siemens circular from May 1958, the company could not begin marketing the device more generally, "because the delivery times [were] still exceptionally long." Customers ordering the scanner at that time could expect to wait around a year for delivery. Therefore, the official launch of the NUCLEOGRAPH, with assembly instructions, technical operating instructions, and everything it entailed, would not follow until 1959.

An offshoot in an optimistic mood

At that time, nuclear medicine was not seen as a discipline of its own but rather as an "offshoot of radiology," according to the memoirs of some of its pioneers. Nevertheless, nuclear physicians around the world were in an optimistic mood. The inventions of the 1950s meant that nuclear medicine procedures could now be put into practice reliably for the first time, and more and more physicians began using tracers in their diagnoses. With this the number of examinations increased rapidly, the first specialized clinics were built, societies and working groups were established, and plans were put in motion to train specialists in nuclear medicine. Further development work was underway in almost every medical discipline, with many individual researchers making their own smaller or larger contributions to the technology's advancement. Sometimes their inventions had a widespread impact on future development, as was the case with the electrical engineer Hal Oscar Anger.

Organs in one piece

There are probably very few people who build their own television from scratch, using parts from the physics lab at their junior college, such as Anger did in the late 1930s. Anger showed exceptional talent from a young age. A radar system he developed during his college days later turned out to be similar to a system that the British developed independently for use in World War II. In his younger years, Anger heard about Ernest O. Lawrence's invention of the cyclotron and about the Radiation Laboratory that Lawrence founded at UC Berkeley in 1931. The laboratory was one of the centers of early isotope research, and its staff included Emilio Segrè and Glenn Seaborg, who jointly discovered the tracer technetium-99m. In 1946, Anger embarked his first day of work at the laboratory.

As an engineer Anger was initially tasked with configuring a newer model of the cyclotron for biological and medical applications, but he also had numerous opportunities to put his own ideas into practice and experiment with new approaches. In 1950, Anger had a simple, yet ingenious idea: by drilling into the crystal of a scintillation detector he created a hollow that was large enough for small tubes to be inserted. This principle allowed radioactive samples to be measured in a virtually loss-free manner. Today, this *well counter* is one of the most widely used instruments in modern physics laboratories. One year later, in 1951, Anger read about Benedict Cassen's invention of the rectilinear scanner and began thinking about possible alternatives.

The rectilinear scanner moved the scintillation counter across the organ being examined in order to create an image of it on a line-by-line basis. The resulting scan was formed from a large number of very small steps stitched together. Anger wanted to build a device that could image an entire organ at once, similarly to a photographic camera, which captures and images everything in the field of view simultaneously. The first prototype, from the year 1952, was built according to the principle of a pinhole camera where the collimator guided the gamma rays toward a crystal where a photographic plate was applied in order to record all of the gamma flashes as dots, with almost complete spatial precision. However, this method was not sensitive enough, and the examination still took far too long.

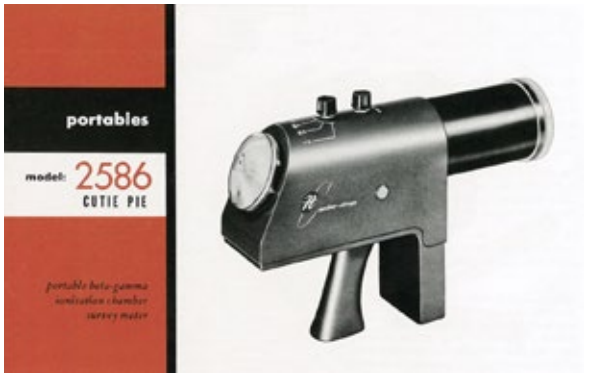
After making a series of improvements, Anger demonstrated his "scintillation camera" in 1958 at

Hal Anger conducting an examination in 1959

the fifth Annual Meeting of the American Society of Nuclear Medicine (SNM), which is now known as the Society of Nuclear Medicine and Molecular Imaging (SNMMI). The audience was captivated. Anger's invention was so sophisticated that it would be several decades before anyone could improve on the basic principle. Inside the camera resided a single large crystal with a diameter of about ten centimeters. Seven photomultipliers on the crystal converted the gamma flashes into electrical signals, and the camera's electronics were set up to calculate the position of the gamma flashes based on a complex system of logic. (To this day, this calculation method is known as Anger Logic.) For the first time, it was possible to image organs such as the liver, kidneys, heart, and brain "in one piece," without having to stitch the picture together from numerous separate measurements.

"Cutie Pie" and gamma camera

Nevertheless, it took a while for the "Anger camera", as it is often known, to reach the market. John Kuranz, who was convinced of the gamma camera's potential, pushed ahead with the device's development until it was ready for market launch. In 1946, Kuranz teamed up with James A. Schoke and Tom Mitchell to establish Instrument Development Laboratories, Inc., which underwent a series of name changes before it began trading as Nuclear Chicago from the mid-1950s onwards. Nuclear Chicago produced radiation-measuring devices such as the "Cutie Pie" and, in 1962, Nuclear Chicago delivered the first commercial gamma camera to William G. Myers, a specialist in internal medicine at Ohio State University. Known as the Pho/Gamma 1, the device was a huge success for Nuclear Chicago yet the gamma camera did not become the standard instrument for molecular imaging until some two decades later. In the mid-1970s many nuclear physicians still favored automatic scanners for certain examinations, partly because they were familiar with the devices and because these devices also delivered reliable results. Undeterred, Nuclear Chicago funneled an increasing amount of research funding into the



The Cutie Pie in a 1955 catalog by Nuclear Chicago

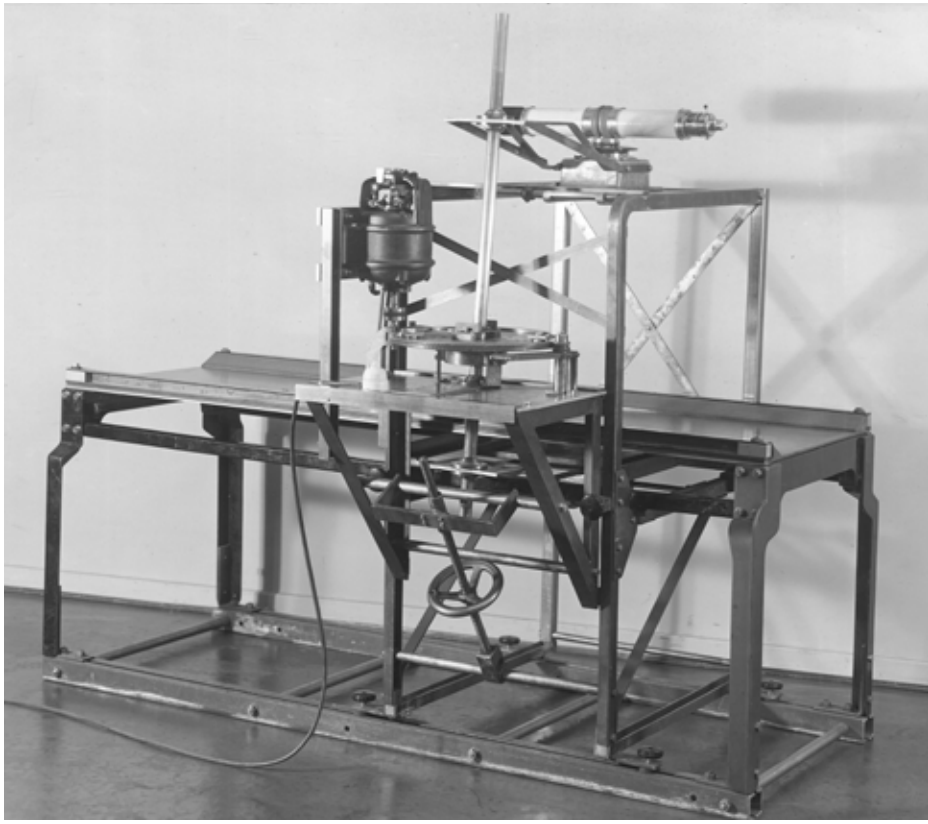
development of gamma camera scanners. The engineers were responsible for many key milestones in the development of modern systems through their work at Nuclear Chicago until the 1970s and subsequently under the umbrella of Siemens Healthineers – but more on that later.

A clear view from every direction

Whether they used scanners or gamma cameras, all molecular imaging systems at that time depicted the patient from a *single* direction, creating two-dimensional scintigrams that showed the distribution of the tracer as the scanner or camera "saw" it from that angle. These so-called planar scintigrams, therefore, suffered from superimposition. To illustrate what this means, let us consider conventional X-ray images, which are subject to the same problem: when a patient's lungs are X-rayed, the rays pass through the front ribs, the lungs, and the thoracic spine before hitting the photographic plate on which the X-ray image is produced. It is impossible to image the lungs in this way without the structures of the bones affecting the result: the same is true of scintigraphy. Two-dimensional images make it difficult to tell whether the metabolic process is taking place in the front or back section of the organ.

These considerations are not important in some diseases – neither for X-ray nor for molecular imaging. Planar scintigrams reveal all of the necessary information in an examination to diagnose hyperthyroidism. For other diagnoses, however, physicians require three-dimensional images that are free of superimposition in order to deliver optimum treatment. In cancer diagnostics, the images must show how much the tissue changed and where the exact location of tumors are. In the 1930s, X-ray equipment was developed to visualize structures inside the body as tomograms, or cross-sectional images. Tomography systems visually "chop the body up" into thin slices. This principle is best explained with an analogy where, if you cut a marble cake into thin slices, you can see exactly how the dough and chocolate are distributed inside.

So-called conventional tomographs, such as the 1934 Siemens Introskop, were the first devices to produce tomograms of the human body without superimposition: the X-ray tube and X-ray film rotated around the part of the body that the physician wanted to examine. At the center of the rotation, where the rays focused, a sharp image emerged of the bodily structures. Outside of the focal area, the image was blurry and poorly defined. The images revealed cross sections of the body with a thickness of just a few millimeters, paving the way for diagnoses that would have been impossible with conventional X-ray images.



The Siemens-Introskop conventional tomograph, 1934

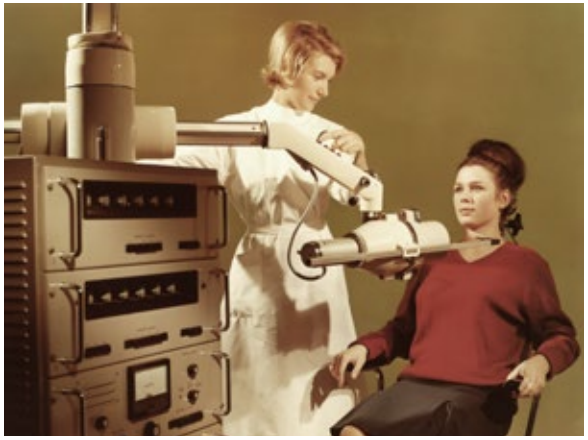
In X-ray technology, these cross-sectional imaging techniques are described as "transmission tomography" because the rays transmit through the body from the outside. In nuclear medicine, the imaging techniques are described as "emission tomography" because the tracer emits the rays from inside the patient. The basic principles of the emission tomography techniques used in nuclear medicine, SPECT and PET, were laid down at the University of Pennsylvania in the early 1960s. David Kuhl, a nuclear physician and a founding member of the Society of Nuclear Medicine, applied the principles of early X-ray tomography to scintigraphy and built various prototypes in collaboration with engineer Roy Edwards. In 1963, they presented their findings in the journal *Radiology*. However, the breakthrough in tomographic imaging was still a long way off. Two key prerequisites were needed for quick and accurate three-dimensional, cross-sectional imaging: the mathematical foundations of image generation, and computers that were fast enough to accomplish the task. For the next ten years, scanners and gamma cameras remained at the heart of molecular imaging.

“Elegance and a fully floating design”

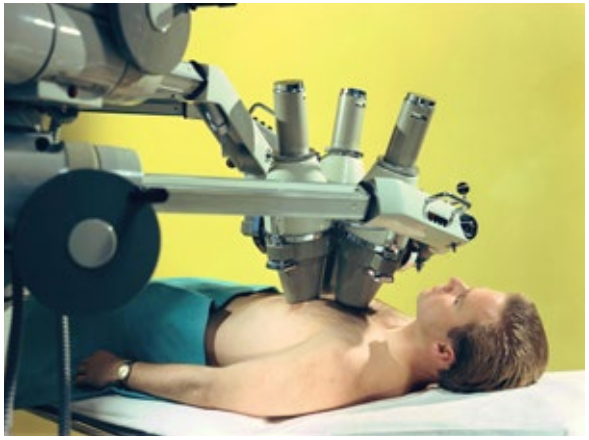
In the meantime, Siemens expanded its nuclear medicine department considerably. In the mid-1960s, two independent development laboratories specializing in molecular imaging were established in Erlangen, one to refine current devices and one to research new technologies. The engineers experimented with state-of-the-art equipment such as computers, monitors, and magnetic tapes for data storage. Technology as a whole, not just molecular imaging, entered a new era. Accordingly, the laboratory reports at the time were replete with questions that would determine the direction of future research: in what situations could a camera replace the scanner? What should a computer for nuclear medicine look like? Where could computers be used?

The innovations of the 1960s were the product of this transitional phase. One obvious example is the NUCLEOPAN product family, to which Siemens regularly added new models between 1961 and 1974. The first model, the NUCLEOPAN 2, was a measuring device that had two measuring heads (hence the “2” in the name) and used a “line recorder” to produce a printout of the examination results. Launched in 1971, the NUCLEOPAN M recorded measurements using either a digital printer or a tape-based pulse storage device. The intervening years saw the emergence of special-purpose devices such as the NUCLEOPAN 3, which measured cardiac activity using three scintillation counters and a built-in electrocardiograph, and the NUCLEOPAN C, which was optimized for the diagnosis of brain lesions. In the typical marketing pattern of the 1960s, one brochure described the NUCLEOPAN family as combining “elegance with clear, technical, functional construction and a fully floating design.”

In 1966, Siemens launched the all-round SCINTIMAT scanner in collaboration with the Italian company SELO. This large, heavily built device could be moved to the patient’s bed in order to print a scintigram of the skeleton, and virtually any organ. The successor model, the SCINTIMAT 2, was much more significant from a technical standpoint and was developed under the project name *Universalabtaster 2* (“Universal Scanner 2”) in Erlangen from 1965 onwards. Up until then, signals detected by the scintillation counter were amplified by electron tubes – evacuated or gas-filled glass tubes that were large and relatively delicate. The electronics of the SCINTIMAT 2 were based entirely on transistor technology, which was in its infancy at the time. Above all, the scanner was designed to ensure the “utmost ease of operation,” according to a development report from 1965: “Through a combination of electronic and mechanical computing elements, physicians and their assistants are to be freed of technical problems relating to radiation measurement and the mechanics of the equipment (scanning speed, adjustment of the recording units).”



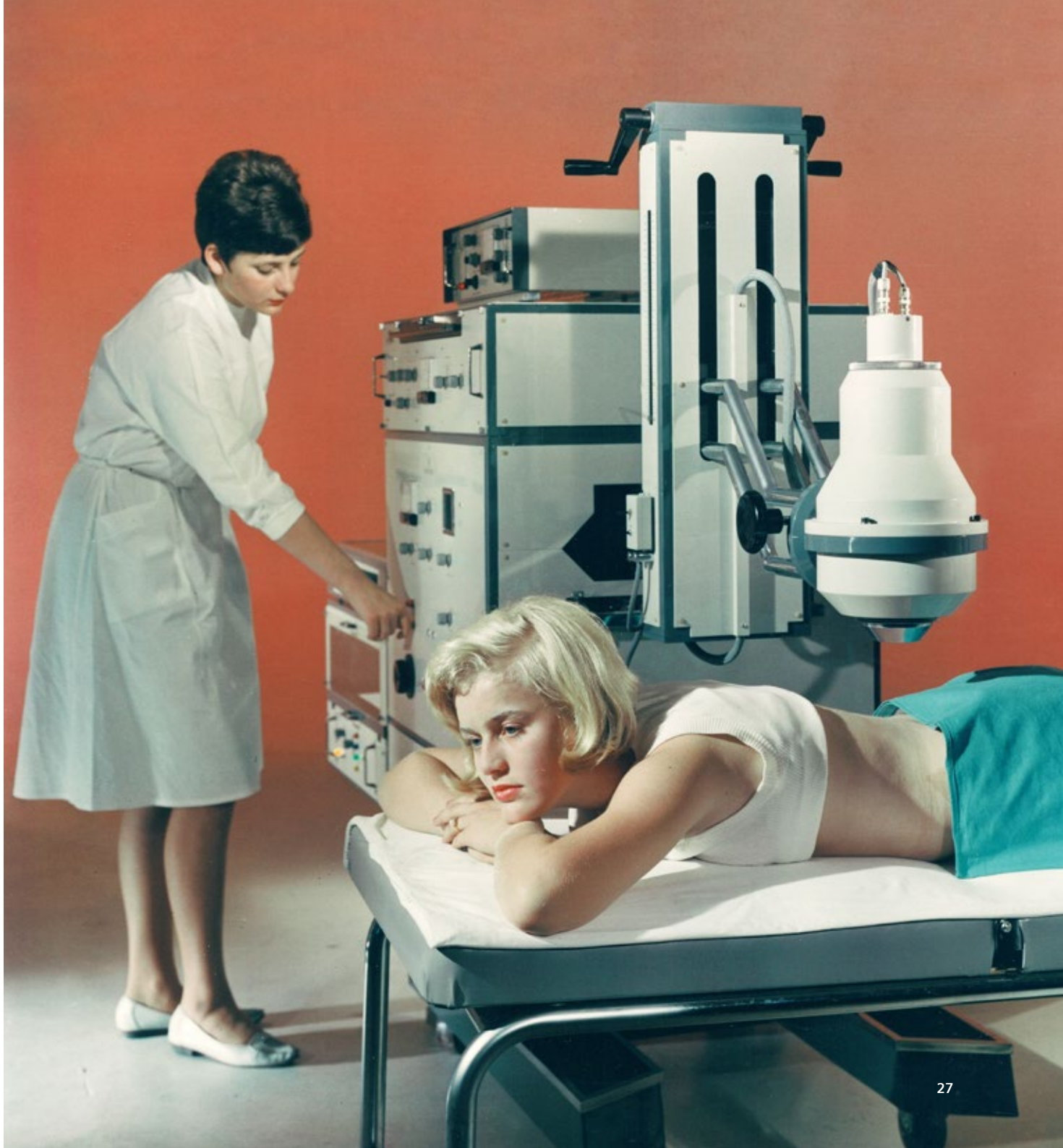
Advertising poster for NUCLEOPAN T from the year 1963



Cardiac examination with the NUCLEOPAN 3 in 1964

The scintigram of the SCINTIMAT 2 was displayed on a “cathode ray display device”

The SCINTIMAT 2 was packed with newly developed technologies. On August 9, 1966, the engineers used the prototype to record the first color scintigram, and in October 1967 they transferred a scintigram directly from the scanner to the memory of a computer for the first time and displayed it on a “cathode ray display device”. The patient data was either relayed directly by the SCINTIMAT 2 or input into the computer using tape cards and punches, which were very popular in the 1960s. Siemens presented the SCINTIMAT 2 to the public at several conferences in 1968, along with other new develop-ments such as the THYREOMAT thyroid measuring device. The SCINTIMAT 2 in particular received “overwhelming interest” according to one of the many euphoric conference reports from that period, with “TV and radio crews reporting from [the] stand and recording interviews.”

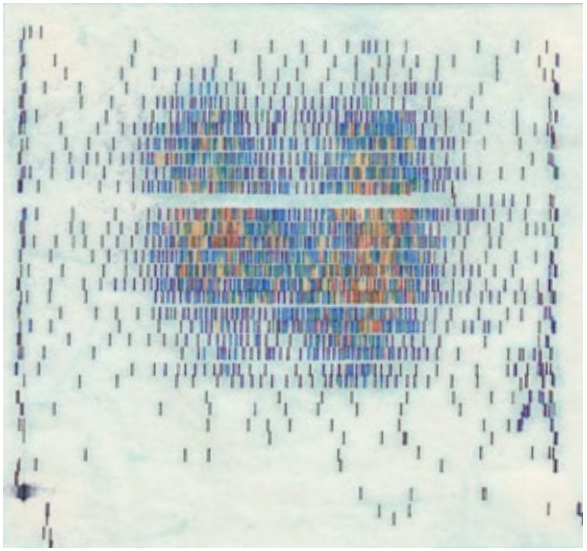


The mobile all-round SCINTIMAT scanner, 1966

Hovercraft under the magnifying glass

In the years around 1970, Siemens engineers in Erlangen developed about a dozen new technologies, including world firsts such as the extraordinarily fast SICOGRAPH ink-jet printer. This printed organ scans true to scale or, in an option requested by many radiologists, as large-format images with dimensions of up to 35 x 42 centimeters. For electronic data processing, Siemens collaborated with the Nuclear Medicine Institute of the German Cancer Research Center (DKFZ) in Heidelberg to develop the SINUC system. This could process all of the data accrued during a hospital stay, from the patient's arrival to the evaluation of measurement results as well as billing and archiving.

In the search for further improvements to imaging technology, Siemens engineers developed a device they referred to internally as the *Röntgen-Lupe* ("X-ray magnifying glass"). In simple terms, this was a combination of X-ray technology and a gamma camera. An X-ray image intensifier, connected to a scintillation counter, multiplied the sensitivity of the X-ray magnifying glass by a factor of three, relative to other gamma cameras at the time. Siemens called the X-ray magnifying glass SCINTICON and extended it with a number of often highly unusual technologies. For example, the patient table was placed on top of air cushions to mimic a hovercraft. The SCINTICON provided outstanding resolution, but its sheer technical sophistication also had a number of disadvantages. Among other things, the apparatus generated enormous amounts of heat and was rather cumbersome to operate. Although it was used at a handful of German hospitals, the SCINTICON never entered mass production. The future would belong to the conventional, and much more practical, concept of the gamma camera.



The first color scintigram taken with the SCINTIMAT 2 on August 9th, 1966

Large-format images printed with the SICOGRAPH ink-jet printer

The SCINTICON stands out in several respects

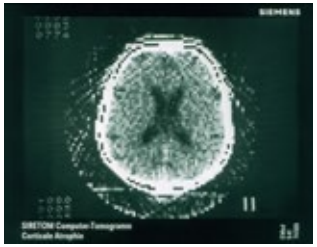
Nine days in an unusual place

By the early 1970s computer technology was powerful enough to generate three-dimensional, cross-sectional images. The first device to produce a tomogram from a 360-degree scan was a computed tomography (CT) scanner based on X-ray technology, yet the first images obtained by CT took around nine days to record. These tomograms were also created in an unusual location. The British engineer Godfrey Hounsfield developed the basic principles of the technology in the research laboratory of the record company EMI. In the initial prototypes, a narrow X-ray beam moved around an object and scanned it slowly from every angle in a large number of individual steps. Once the measuring time was shortened to a few minutes, the first patient brain was scanned using the new procedure on October 1, 1971. Hounsfield presented his research to the public and triggered a veritable epidemic of "CT fever". From then on, computed tomography evolved into one of the most important diagnostic procedures in the world of medicine. In recognition of his pioneering work, Hounsfield received the 1979 Nobel Prize in Medicine. He shared it with the American physicist Allan M. Cormack, who separately produced a mathematical description of the behavior of X-rays in the human body between 1957 and 1963.

In 1972, Siemens established its own CT development department with the aim of building a powerful CT scanner optimized for workflows at hospitals and healthcare facilities. The first CT scanner from Siemens, the SIRETOM cranium scanner, launched

in 1975. Just two years later, the technology made its first big leap forward in the form of the SOMATOM whole-body scanner. Whereas the SIRETOM captured two slices of the brain in about four-and-a-half minutes, the SOMATOM could do the same in eight seconds. At first, computed tomography and molecular imaging developed largely independently of one another, but then their paths crossed at the turn of the millennium.

The inventor of computed tomography (CT), Godfrey Hounsfield, 1975



A head scan using the prototype of SIRETOM, 1974

SIRETOM pre-production model in 1975

The Nuclear Chicago Pho-Gamma in 1972

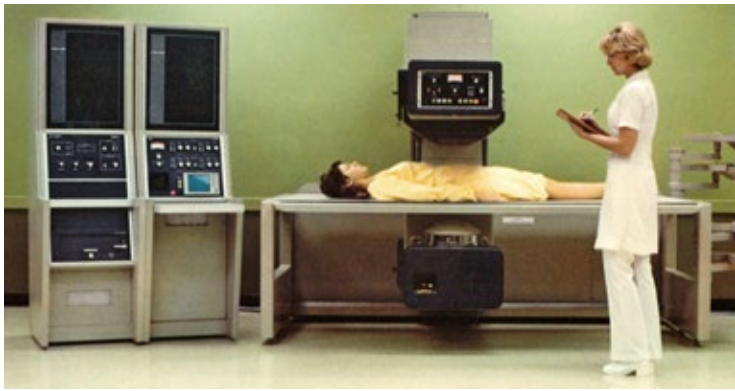
From Erlangen to Chicago

The 1970s was one of the most interesting decades in the history of medical technology. Microelectronics enabled the development of new technologies, which made the equipment more versatile and diagnostics more reliable. Almost all of the key techniques in modern medical imaging had their beginnings, or were on the cusp of a breakthrough, in this decade. The first CT scanners were installed at hospitals and healthcare facilities, ultrasound diagnostics experienced its first major boom, magnetic resonance imaging was in the starting blocks, and molecular imaging would soon be on everyone's lips. At Siemens, the priority afforded to these new developments led to a number of changes as the headquarters of the medical technology division in Erlangen became the hub for magnetic resonance imaging, and computed tomography activities were also initially concentrated here before undergoing significant expansion at a new factory in the nearby town of Forchheim a few years later. With a goal of boosting worldwide sales and expanding the development of ultrasound diagnostics and nuclear medicine, Siemens began looking for experienced reinforcements in the late 1970s. It would ultimately find them in the third-largest city in the United States, Chicago.

Advertising photo of the Micro Dot Imager from 1973

From 1970 onward, Nuclear Chicago, the manufacturer of the first commercial gamma camera, had been part of Searle Radiographics Incorporated, a subsidiary of the American pharmaceutical group G.D. Searle & Company. Usually referred to as Searle for short, the company was building some of the most advanced ultrasound systems in the world, complete with microprocessors and initial forays into digital signal processing. In the field of molecular imaging, Searle – or, to be precise, Nuclear Chicago, because the company kept its own name until the mid-1970s – developed a whole series of innovative and influential technologies.

In 1975, the Pho/Gamma LFOV was the first large-field gamma camera. Large-field-of-view (LFOV) technology delivered more detailed images from inside the patient's body than conventional gamma cameras. This was thanks to completely redeveloped electronics, albeit still based on the principles set out by Hal O. Anger. According to an advertising brochure in 1973, the system's Micro Dot Imager replaced "the expensive and tediously inaccurate pulling of Polaroids" with a display console. Complete with LED status indicators, a novel feature in those days, the system could record up to 80 high-resolution images on one large X-ray film if necessary. In combination with the Micro Dot Imager, the Pho/Gamma LFOV was particularly well suited to routine examinations thanks to its quick and easy operation. As a result, it established itself as the "workhorse" of many nuclear medicine facilities over subsequent years.



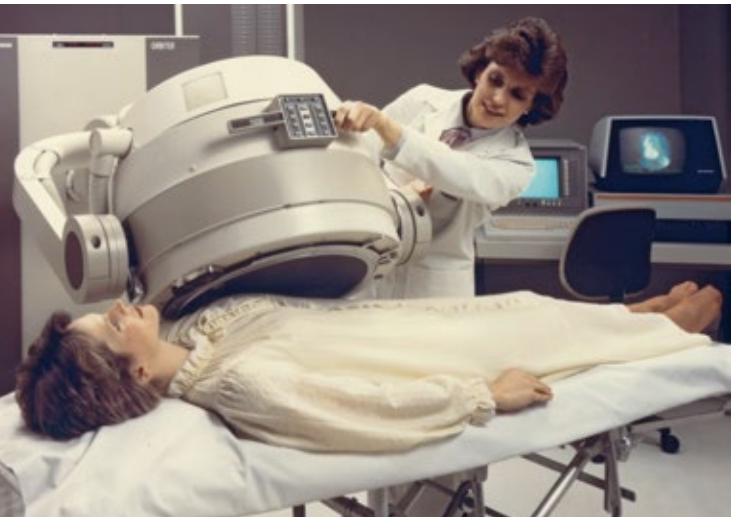
The first tomographic system in molecular imaging, the PHO/CON Tomographic Multi-Plane Scanner, 1977

Engineers in Chicago also developed two systems that could produce tomographic images using very different technical principles. The PHO/CON Tomographic Multi-Plane Scanner was the first tomographic system in the field of molecular imaging with two gamma cameras built into a stand – one above the patient table and one below – that simultaneously recorded twelve cross-sectional images of the inside of the body. The images were still quite blurry, but they allowed physicians to identify the location of metabolic processes for the first time. Soon afterwards, Searle launched a *single-camera* tomography system that differed from the PHO/CON in one key respect: its camera revolved around the patient, making the Orbiter the first conventional SPECT system in the history of Siemens Healthineers as Searle sold its nuclear medicine and ultrasound medical technology divisions to Siemens in 1979 during restructuring measures. From March 1980 onward, Searle Radiographics was known as Siemens Gammasonics, Incorporated.

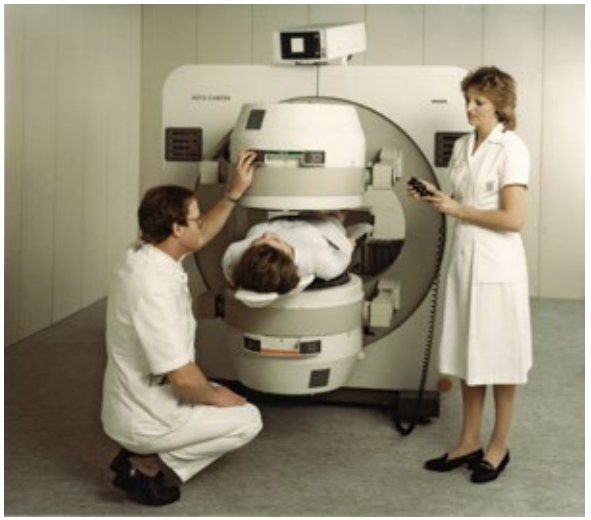
Dual cameras improved scan sensitivity

Working under the Siemens umbrella, the engineers developed the next generations of tried-and-tested equipment. The Siemens Orbiter was a bestseller in the 1980s, and models can still be found in use at some healthcare facilities today. At that time, the development of new technologies increasingly focused on the promising technology known as SPECT. The first major step toward modern SPECT systems reached the market in 1981 in the form of the Siemens ROTA camera, the world's first commercial system with two rotating gamma cameras. Thanks to its second camera, the system boasted double the measuring sensitivity. Depending on the region of the body that was examined, this provided a range of benefits including a reduction in scan time and the potential to reduce tracer dose or boost image contrast. The ROTA camera could also be used for conventional planar scintigraphy with a single gamma camera and, the basic structure of the device already corresponded to that of today's SPECT systems.

The 1980s brought rapid and fundamental changes to the inner workings of these systems. Sixteen-bit processors allowed SPECT data to be processed on the fly, that is, while the system was still scanning the patient. The examination results were stored on hard disks with what was, in 1985, an impressive capacity of 80 MB. Analysis consoles such as the Siemens SCINTIVIEW SP or the Siemens MaxDELTA offered numerous programs and functions designed to assist the operator. Physicians could rotate and magnify the images and display them as a video in "cinema mode". By the mid-1980s, there was already a surprisingly long list of standard and optional software, including specialized programs for imaging the lungs, liver, or heart. The operator could access detailed help screens to assist with any questions, and the system included initial forays into automatic quality control.



A bestseller in the 1980s: the Siemens Orbiter



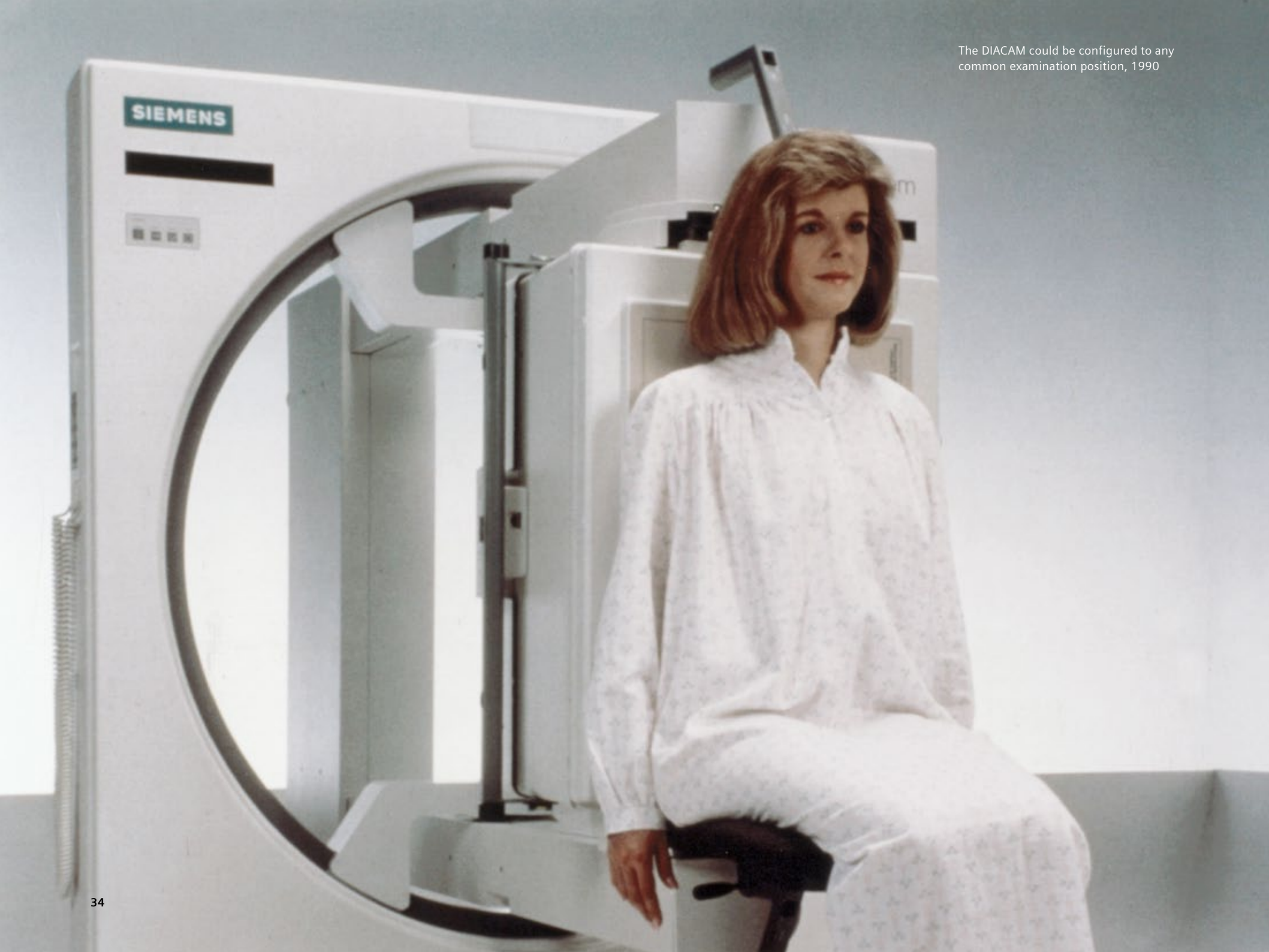
The Siemens ROTA camera, the world's first commercial system with two rotating gamma cameras, 1981

In the 1980s there was additional equipment that was optimized for specific examinations

A matter of form

If we compare current scanners with those of the 1980s, one thing stands out in particular: all of today's gamma cameras, or SPECT systems, from Siemens Healthineers are very similar in terms of their basic structure. Over the years, the engineers developed a system architecture with considerable mechanical flexibility that is just as well suited for examining small organs as it is to imaging the whole body. In the 1980s, however, the scanners still differed significantly from one another in terms

The BODYSCAN gamma camera was developed specifically for whole-body examinations, 1987



The DIACAM could be configured to any common examination position, 1990

of their form and mode of operation. At that time procedures often benefited from, or even required, additional equipment and scanners that were optimized for specific examinations. For example, the additional OSTEOMAP hardware was coupled to the Orbiter gamma camera to make bone density measurements much more precise and cost-effective, and reduce the scanning time by half.

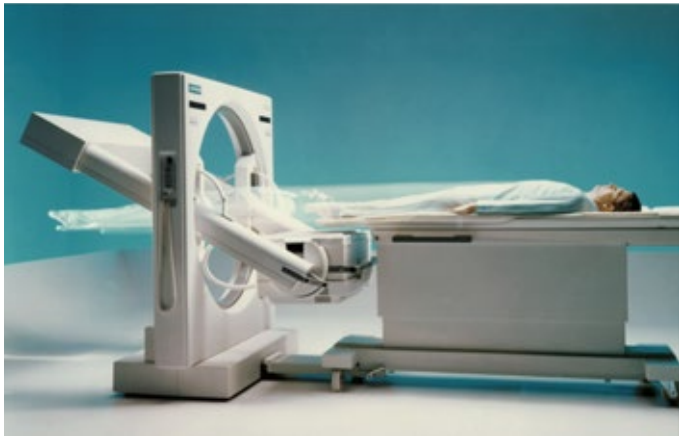
Another exceptionally fast device in its own area of specialization was the BODYSCAN gamma camera, launched in 1987. Siemens developed the system specifically for whole-body skeletal examinations, which searched for tumors and metastases over a wide area. Moreover, the BODYSCAN examined the patient's body three times faster than any other gamma camera at the time. This was thanks partly to its mechanical structure and partly to the innovative measuring system: its two detectors were the largest gamma cameras ever used, providing a metering area wide enough to image large adult males, including their arms, in a single pass.

A question of balance

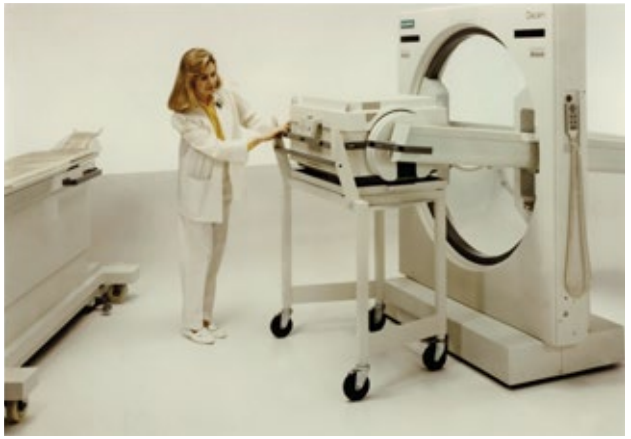
At first glance, the DIACAM-Body SPECT, from 1990 looked like a cross between several special-purpose devices. Its system architecture earned the device an iF Design Award and allowed it to perform scintigraphy, SPECT, and whole-body examinations at the same standard as specialized instruments. On the gantry, the gamma camera and gantry arm could be configured to any position independently of one another, regardless of whether the patient was lying in a hospital bed, sitting in a wheelchair, or standing. The technology installed in the system included a whole range of unique innovations, such as the electromechanical-coupling mechanism that connected the patient table and the gantry without the need for an additional cable.

The assisted collimator changer and the AUTOFORM collimator were two new features of the DIACAM that stood out in particular. The technician chose the most suitable collimator prior to each examination, primarily based on the sensitivity of the gamma camera, the image resolution, and the tracer dose. Previously, changing the lead apertures had been the most strenuous aspect of examination preparation. For example, the DIACAM's all-purpose collimator weighed in at 40 kilograms, and the high-energy collimator for the use of high energy gamma radiation, tipped the scales at 187 kilograms. With the DIACAM's collimator-changing technology, operators could switch between collimators effortlessly without the time-consuming manual adjustments necessary in the past. Staff moved the corresponding collimator trolley up to the gamma camera, which had a sensor for identifying the collimator's weight and type. Visual and acoustic signals then helped the operator make the few adjustments that were still required. The DIACAM's Auto Balance facility automatically balanced out the weight difference, up to 147 kilograms, using motorized counterweights.

Collimators have a greater influence on scan quality. The shape of the separating walls between the holes – technically referred to as *septa* – affects the sensitivity, image resolution, and required radiation dose. In conventional collimators, the varying thickness of the septa reduces the sensitivity, meaning that the patient must either receive a higher dose of radiation or endure a significantly longer scan. Instead, the septa in AUTOFORM collimators, which were used for the first time in the DIACAM, had a uniform thickness at every point of the collimator. As a result, they were then, and still are, the most sensitive SPECT collimators on the market. The abbreviation LEHR, often seen in relation to AUTOFORM collimators, stands for "low-energy, high-resolution."



The DIACAM allowed it to perform scintigraphy, SPECT, and whole-body examinations at the same standard as specialized instruments



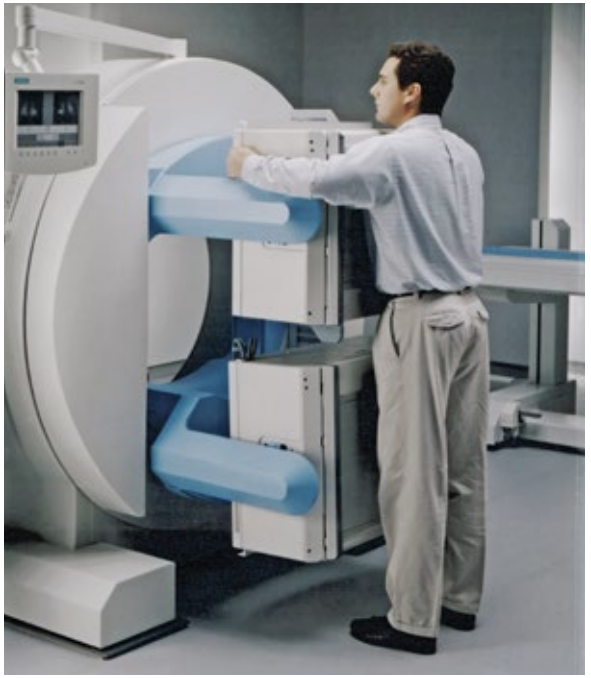
DIACAM's collimator-changing technology helped operators switch between collimators effortlessly

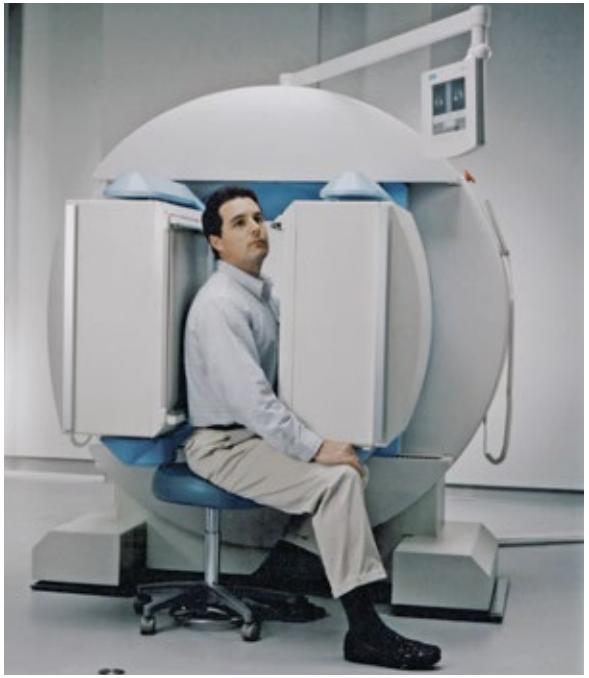
E for emission tomography

With the DIACAM, the Siemens engineers in Chicago earned themselves the prestigious Design Award, yet with the E.CAM system, it was largely Siemens customers who were to thank for the iF Design Award (Best in Category – Medical Technology). From the conceptual design phase onward, numerous users from various technical disciplines had a major influence on scanner development with their ideas, wishes, and requirements. This joint design process centered around clinical benefit, productivity, cost efficiency, and future viability with the objective to make work easier for radiology staff and examinations more comfortable for the patient.

This approach gave rise to an extremely flexible system architecture that closely resembled the basic structure of today's SPECT systems from Siemens Healthineers. Launched in 1996, the star model of the E.CAM family was known as the E.CAM Dual-Detector Variable-Angle system and was followed a few months later by an entry-level model with a single gamma camera and slightly slimmed-down dual-detector system for routine diagnostics. The fourth model in the E.CAM family, a system which can also detect the annihilation radiation during PET imaging, was available either as a stand-alone system or as an upgrade for the dual E.CAM cameras.

All four E.CAM models featured a wealth of technical details that, taken together, considerably improved the quality of examinations and the resulting images. The measuring system was based on a simple concept: the smaller the distance between the patient and the gamma camera, the sharper and more detailed the image. In a unique feature at that time, the patient table was just 2.5 millimeters thick and therefore 20 times thinner than conventional tables, putting the patient 50 millimeters closer to the gamma cameras in every scan. Many other technologies that remain significant to this day were also installed for the first time in the E.CAM family. For example, body contouring sensors ensured that the newly developed digital Siemens HD detectors were in an optimum position relative to the body.



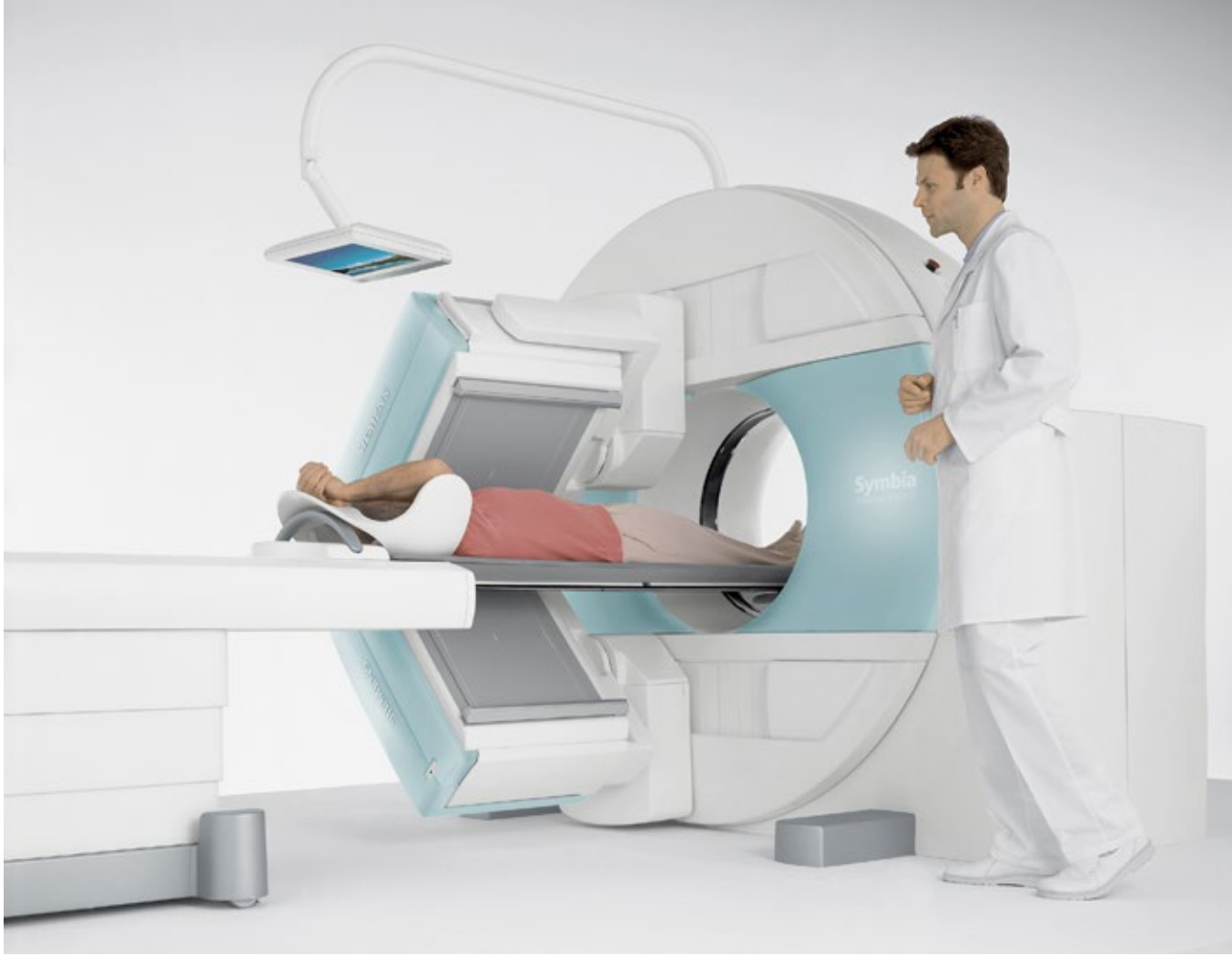


The flexible system architecture of the E.CAM from 1996 closely resembled the basic structure of today's SPECT systems from Siemens Healthineers

2 – 1 = 3, 4, or 5

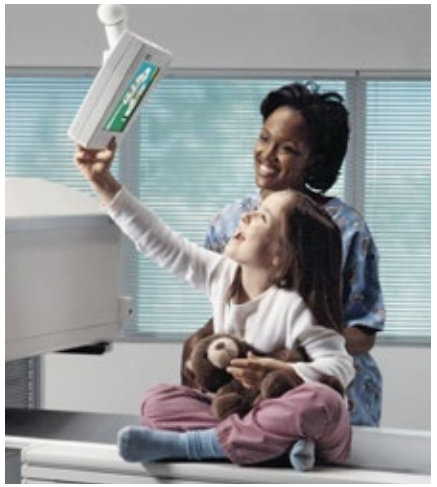
At the turn of the millennium, Siemens systems were equally suitable for planar scintigraphy, whole-body and SPECT examinations, and even outperformed dedicated systems from a few years ago. However, many diagnostic checks still required the physician to compare the results of SPECT scans with CT images, such as in the case of bone metastases. When it came to where *exactly* the lesion was located and configured, the two adjacent images only allowed doctors to make an estimate. This procedure also required considerable patience on the part of the patient, who not only had to be transferred from the SPECT to the CT scanner but also had to endure two separate exam preparations. Worse yet, scans sometimes had to be repeated if the transfer between scanners led to insufficient matching between the two images. A combination of SPECT and CT would therefore save a great deal of time, for the staff and the patient, as well as being far more accurate.

In the early 2000s, Siemens developers examined whether a hybrid SPECT/CT scanner could be created without compromising performance. A team of engineers from the areas of nuclear medicine and computed tomography combined the latest version of the E.CAM with a multi-slice CT scanner, developed in Forchheim, to create the SPECT/CT TruePoint Symbia, the first system in today's Symbia™ family. This hybrid of two technologies combined three imaging procedures – or even four or five depending on the definition – into one system. The system could perform combined SPECT/CT scans, as well as standalone SPECT or CT scans and, like all Siemens SPECT systems at the time, was capable of recording planar scintigrams and whole-body images. Both the molecular images and the CT scans were of the same standard as those produced by dedicated systems. The CT component was the SOMATOM Emotion, a device that also won an iF Design Award. All upgrades and improvements to this CT scanner were seamlessly incorporated into the hybrid Symbia family.



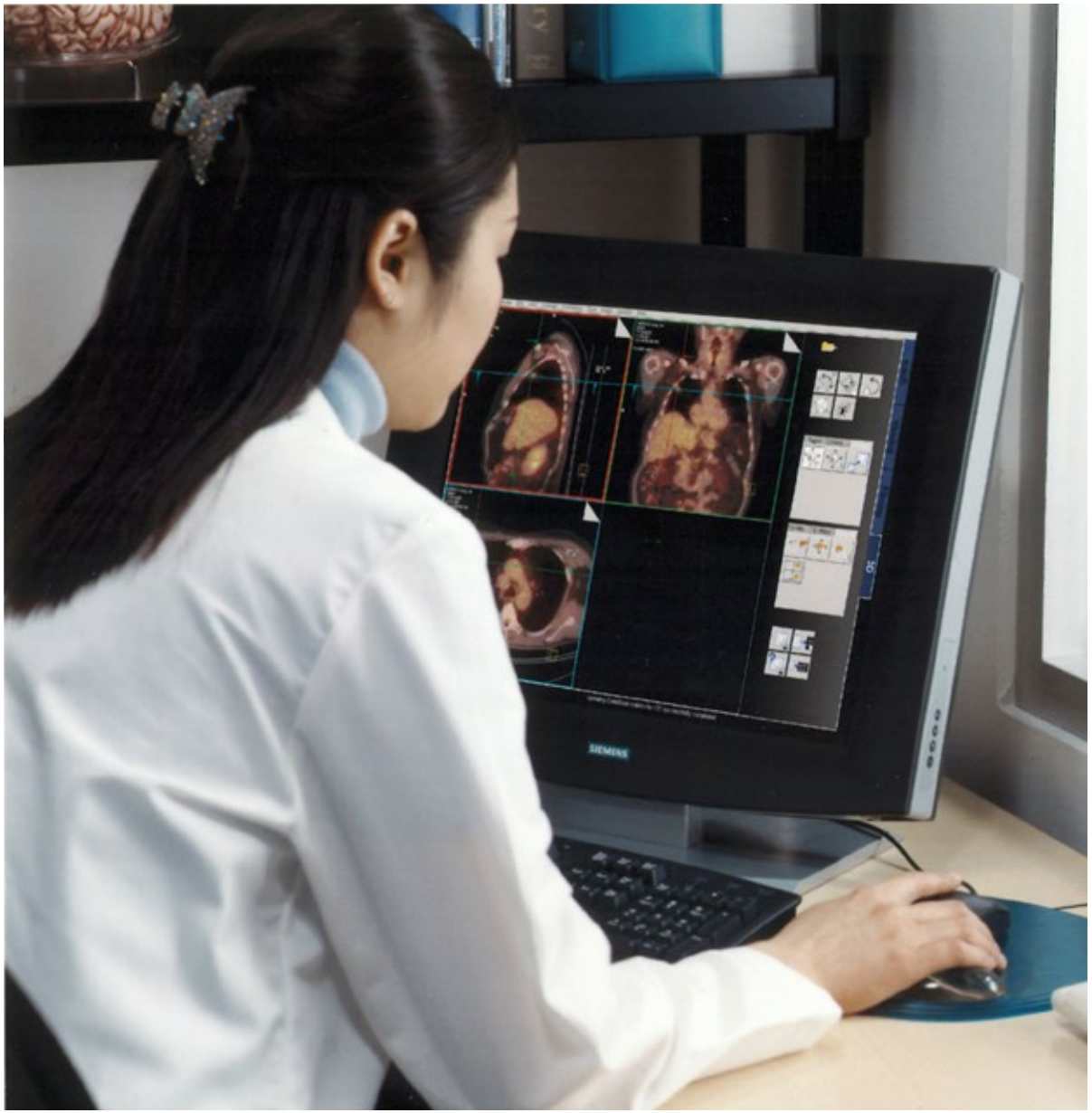
SPECT/CT TruePoint Symbia, the first system in today's Symbia family, 2004

Particularly on the software side, a great deal of progress was made within the space of a few years. In this respect, the first version of the E.CAM SPECT system and the TruePoint Symbia SPECT/CT were scarcely comparable. Symbia used the *syngo* software that Siemens adopted in 1999 to



The new e.media patient comfort system included a touchscreen, 2004

standardize the operation of all its systems, making it the first medical technology manufacturer to do so. The graphical user interface consisted entirely of self-explanatory symbols. Beneath the surface, *syngo* contained a vast library of programs, some of which were highly specialized. For example, the *Flash 3D Iterative Reconstruction* software feature leads to an improved image quality in comparison to older standard processing. This boosted image contrast by up to 24 percent relative to other computational methods. For CT scans, the Combined Applications to Reduce Exposure (*CARE*) program calculated the lowest possible dose for each patient while ensuring optimum image quality: dependent on the patient's anatomy, CARE could reduce the radiation dose by up to 56 percent. When the TruePoint Symbia SPECT/CT was launched in 2004, the company offered an e.media patient comfort system that included a touchscreen. With a 15-inch screen connected to a DVD player, e.media was intended to help patients relax during the scan.



Siemens developed the *syngo* software to standardize the operation of all its systems, 1999

A new name and the first addition to the family

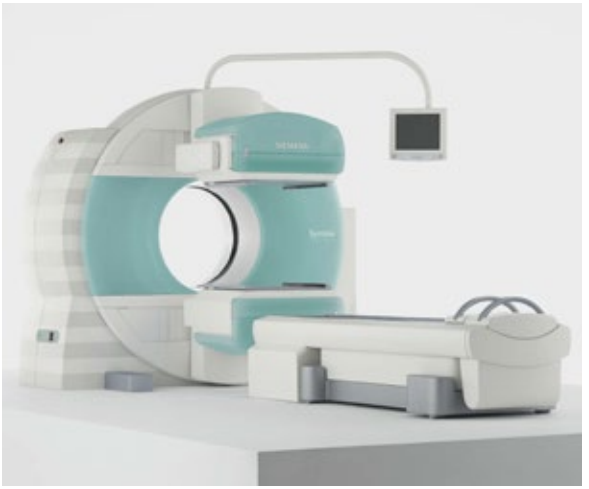
This system architecture laid the foundation for numerous developments over subsequent years. In 2005, soon after the Siemens Nuclear Medicine division was renamed Siemens Molecular Imaging (MI), the Symbia platform welcomed the first new addition to the family. The Symbia S was a dedicated SPECT scanner equipped with all the familiar MI technologies from the TruePoint Symbia. Designed as a modular platform, the system was therefore open to new developments in the future.

From as early as 2006, two major innovations were available for incorporation into Symbia models. With the first, the collimator was now changed automatically with no need for manipulation or scrutiny by operating staff. For the first time, Symbia also provided fully automatic quality control, which allowed for regular testing of the detector calibration. In the past, these tedious, and time-consuming, tests took between 20 and 60 minutes and were manually performed on a daily basis. Now, the Automated Quality Control function ran the tests overnight and forwarded the results to the technician, who could read through them in comfort at their desk the next morning.

A matter of the heart

Accurate and reliable examinations of the heart are particularly important in medicine as this organ is the origin of many physical complaints. Symptoms such as shortness of breath or cardiac dysrhythmia can be a direct result of metabolic disorders, such as constricted coronary vessels that impede blood flow. One major strength of SPECT lies in its ability to aid in the diagnosis of such disorders. At this time, a Symbia system could visualize circulation in the cardiac muscle in about 20 minutes. The images it produced were meaningful, but their quality could not be improved using existing technology as the image resolution was physically limited by the number of photons arriving at the crystals of the gamma camera.

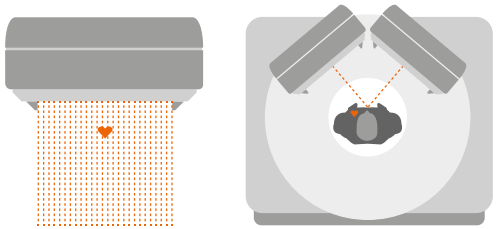
IQ•SPECT technology bypassed this limitation with a combination of a specialized collimator (SMARTZOOM) and optimized software algorithms. The SMARTZOOM collimator increases the sensitivity for the heart in the rotation center without cropping of the imaged volume. All bores of the collimator have their individual direction and this is described in a "vector map". This map is included in the tomogram reconstruction. The reconstruction algorithm uses a thorough description of the imaging process in order to improve image quality. All of this boosted the sensitivity of the measuring system by up to a factor of four in respect to the heart. IQ•SPECT provided physicians with far greater flexibility when it came to adapting the examination to the patient and to the specific medical problem. The Symbia system



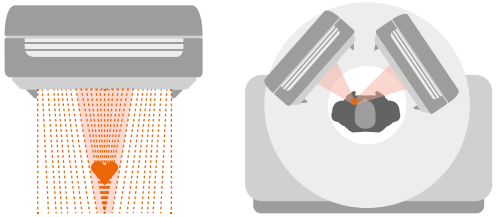
Symbia systems were designed as a modular platform

could scan a patient's heart in four minutes using a standard tracer dose. An eight-minute scan needed only around 50 percent of the usual dose, while a 16-minute scan time allowed the dose to be reduced by as much as 75 percent.

Conventional SPECT/CT



Siemens IQ•SPECT (SMARTZOOM)



Up to 75 percent less dose injected

Turning the tables

There were two major limitations of SPECT/CT until 2012. On the one hand there was a significantly lower spatial resolution of the SPECT component when compared to the CT. Therefore disease processes could be located with a limited precision. On the other hand tomographic SPECT images provided only relative numbers about the distribution of the tracer and the underlying biological processes, however the absolute amount (activity) of the tracer in the tissue was unknown. As a consequence the same was true in respect to the biological processes.

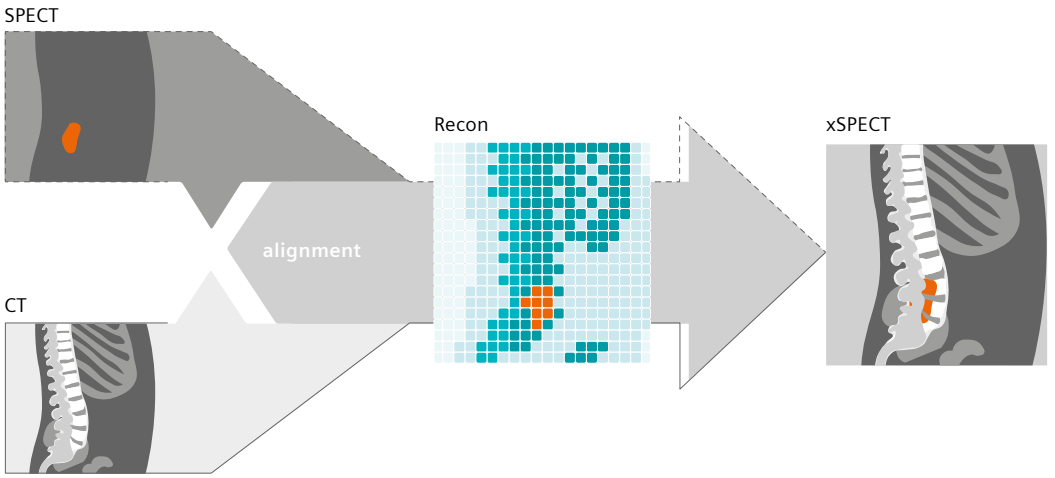
In 2012 this changed with the advent of the xSPECT family of products. The base – like in IQ•SPECT – is a much more detailed description and modeling of the image formation process during the acquisition. This knowledge about system properties is then used for the calculation of the slice images. Examples are the use of the more precise coordinate system of the CT, the acquisition of the SPECT in a finer matrix and therefore in a potential higher resolution, the exact description of the collimator properties and an improved determination of the position of both camera heads. Calculation rules for low signal intensities were obeyed. Overall this leads to a much more precise computing of the tomograms (reconstruction).

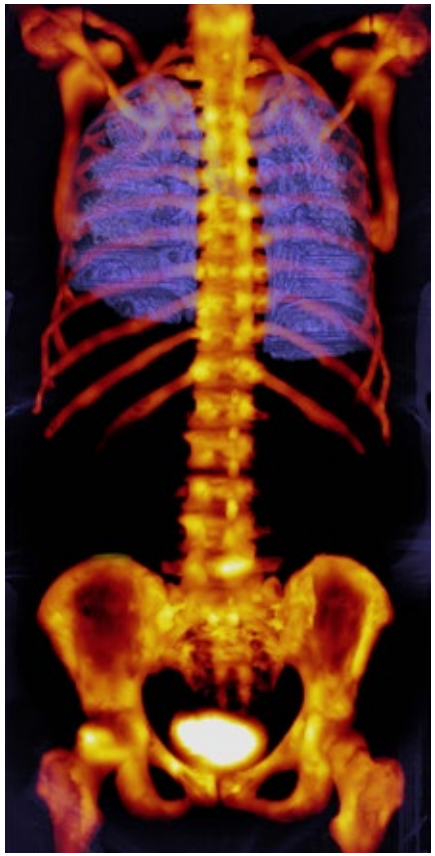
The new camera generation Symbia Intevo integrated these methods in a clinically useful system. The first xSPECT family member "xSPECT bone" improves image quality of bone scans in a dramatic way. The idea behind is, that the CT is not only acquired for attenuation correction and support of the reading process – like it became standard the few years before – but also directly supports the SPECT reconstruction with its higher resolution. It is very simple to differentiate bone from other tissue types via CT. Five tissue classes are defined and integrated in the SPECT reconstruction. This results in sharp bone contours in the SPECT. The physician is able to delineate and interpret disease processes in the bone in a better way.

The second xSPECT family member "xSPECT quant" enables the precise measurement of activity concentrations (tracer content) in the tissue. Precise standard radioactive sources calibrate the gammacamera and together with the improved reconstruction slice images of absolute aciticty concentrations can be achieved (in Bq/ml instead of counts). xSPECT quant simplifies all necessary steps and takes care in respect to reproducibility across different scanners of the same family. A laborious manual calibration and postprocessing is avoided, which would be depending on the diligence of the user. A standardized absolute quantification, which had been a common feature of PET since many years (see the following chapter) is now available in a simple way also for SPECT. This allows the calculation of further parameters. This quantification enables the physician, to evaluate the course of a disease with a higher precision than with the human eye alone and provides the foundation for the treatment with radioactive drugs. A more accurate planning and control of therapy is possible. Experts call this "dosimetry".

The new word "theranostics" describes a concept, which connects in a seamless manner diagnosis and therapy using the same biological process.

SPECT/CT





xSPECT is a combination of special hardware and mathematical algorithms for image generation

The first system with xSPECT technology was the Symbia Intevo SPECT/CT

This enables an optimized individual therapy. Molecular imaging can be crucial to support this concept. Standardized quantification of xSPECT quant allows to plan treatment with high precision and to follow up its effects. xSPECT quant technology enables Siemens Healthineers to lead the way in the developments of the next years.

Then and now

All of the current systems in the Symbia family from Siemens Healthineers use the same basic technology. The SPECT images are acquired using HD detectors and AUTOFORM collimators and reconstructed using software algorithms such as Flash 3D iterative reconstruction, for example. Depending on the customer's needs additional options could be added like patient entertainment system e.media, automatic collimator changer, integrated ECG, automatic quality control or the solution IQ•SPECT for cardiac scans. Today, the possibilities for adjusting the detector position are virtually unlimited.

All patients, regardless of their weight or size, can be examined in almost any conceivable position.

A great deal has also changed from the patient's perspective. Some feel claustrophobic when they're in the "tube," while others feel uneasy at the very sight of it. For these patients in particular, examinations are much more pleasant than they once were. With the Symbia Evo Excel, which was introduced in 2015 and is the most compact SPECT system on the market, the progress is clear to see: the gantry aperture has grown from 86 to 102 centimeters, and the length of the tunnel has shrunk from 59 to 34 centimeters. This gantry architecture helps patients tolerate undergoing a scan. The same applies to the patient table. Whereas older E.CAM models could scan patients weighing up to 180 kilograms, the Symbia Evo Excel can support weights of up to 227 kilograms.

Among other features, the CT component of all modern Symbia SPECT/CT systems is equipped with features aimed at minimizing patient dose. For example, *CARE Dose4D* automatically adapts the dose to the patient's body during the scan, and the versatile X-ray tube configuration can be optimized to examine children. The current high-end system Symbia Intevo Bold, which Siemens Healthineers presented to an audience of nuclear medicine experts at the 2017 Annual Meeting of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), is the first of its kind to be equipped with the *Sinogram Affirmed Iterative Reconstruction* (SAFIRE) and *Iterative Metal Artifact Reduction* (iMAR) algorithms. SAFIRE reduces the radiation dose by up to 60 percent for the same image quality, while iMAR reduces artifacts caused by metal objects in the body, such as dental implants or artificial hips.

Today, the global headquarters of Siemens Healthineers Molecular Imaging can be found in Hoffman Estates, Illinois, around 50 kilometers north-east of downtown Chicago. Here, the engineers develop all Symbia SPECT and SPECT/CT scanners, as well as the corresponding software, in close collaboration with numerous physicians and scientists around the world and computed tomography colleagues in Forchheim and Shanghai. The current Symbia systems are the result of over 60 years of innovation, in which time molecular imaging evolved from a simple measuring station for thyroid examinations into one of the most versatile imaging procedures in modern medical technology. From the outset, Siemens Healthineers and its precursor companies have been responsible for numerous milestones in development that helped shape the technology we know today.

SPECT examination at the bedside

Marketing image for Symbia Intevo SPECT/CT, 2013

Siemens Healthineers presented the current high-end system Symbia Intevo Bold in 2017

Over the last two decades, SPECT has almost completely replaced purely planar scintigraphy, and almost half of all imaging departments now work with SPECT/CT systems. Together, PET/CT, SPECT, and SPECT/CT scanners, now cover all of the diagnostic capabilities of nuclear medicine. The stories of both SPECT and PET can be traced back to the early days of scintigraphy. Then, from the mid-1970s, the two techniques began to specialize and PET adopted an interesting approach from more than just a technical perspective.

The Symbia Evo Excel from 2015 is the most compact SPECT system on the market

The biographers of the body

From rudimentary laboratory equipment to today's high-end PET/CT systems

The history of positron emission tomography (PET) is, in a sense, both a subplot and a sequel. The basic principle, i.e., depicting metabolism using tracers, is the same in PET as in classical scintigraphy and SPECT. The technical implementation is also based on the same process: first, the gamma rays emitted by the body are converted into light beams, which are then converted into electrical signals containing precise information about the amount of metabolic uptake and place of origin. Based on these values, a computer generates the clinical images. All three processes of molecular imaging thus share the same historical origins. Having said this, certain events are more important in the evolution of some procedures than others. The invention of the cyclotron, for example, only played a peripheral role in the history of SPECT, but it was a crucial development for PET; to this day, many PET tracers are still produced using this technology. The actual differentiation of molecular imaging began in the 1970s. SPECT started, at first gradually but then more rapidly, to supplant conventional scintigraphy devices. Then there was PET, another very promising method, whose innovative technical framework gave it the potential to develop its own unique strengths.

From a technical perspective, the evolution of PET was one of the most impressive developments in the history of medical technology. This much is apparent even from a relatively superficial comparison. In 1976, anyone who wanted to count the detector elements of a PET scanner could do so in about a minute; today you would probably need at least ten hours for this. ECAT II, one of the first commercial PET systems, used 66 detectors to map the distribution of a tracer, whereas the latest Biograph™ Vision PET/CT works with 60.800 detectors. As with the history of many technologies, the initial phase of this development was influenced by a number of individual researchers experimenting with new methods in their laboratories. It was not long before clinicians and engineers also became part of the process by applying the procedure in their practice and developing it further. But why make all this effort? Was it really necessary to develop yet another molecular imaging procedure? And what exactly was the big difference between PET and SPECT?

PET is the most accurate method of depicting metabolic processes. The unrivaled sensitivity of PET systems is not thanks to the aforementioned number of detectors alone; the system architecture and physical characteristics of the positron annihilation also play a key role. The main difference between PET and SPECT is how they acquire data: SPECT maps the precise distribution of the data because its collimator only allows radiation through that comes from a certain direction, meaning the photons are filtered. The PET system, in contrast, does not require any collimator because the photons produced by the positron annihilation propagate in a straight line and strike the detector ring virtually at the same time (a coincidence event). The gamma rays from the tracer reach the PET detectors almost unimpeded and unchanged. This leads to a much higher sensitivity of the system compared to SPECT. The precise measurability of the positron annihilation in the detector ring and the accuracy of the photon count (the technical term for this is *quantification*) are the principle reasons for the strengths of the PET system. The PET technique is preferable when a clinician needs a particularly accurate and high-resolution depiction of a patient's metabolic processes in neurology, cardiology and oncology. Cancer diagnostics was and is, one of the most important drivers for the use of positrons in medicine.

In line with the brain

Thanks to modern imaging techniques, we can observe human thought processes and emotions, we can accurately identify malfunctions and pinpoint the location of tumors within a few millimeters. As early as the first half of the 20th century, we were able to visualize the brain using X-rays. However, hemorrhages or tumors are often virtually impossible to detect in conventional X-ray images of the skull because the cranial bones superimpose and overshadow the soft brain tissue. The process also required elaborate preparation, which was strenuous for the patient. The conventional methods available at the time meant that the system could only depict cranial vessels with the help of contrast agents.

To acquire images of the cerebral ventricles, air was introduced to displace the cerebrospinal fluid. After such a lengthy and painful procedure, the patient generally spent several days in hospital.

In 1950, when even conventional scintigraphy was still very much in the nascent stages of development, the respected physician Gordon L. Brownell began working on how to improve brain scans with the help of nuclear medicine. Brownell discussed various methods with William Sweet, chief of the neurosurgical service at Massachusetts General Hospital, and proposed the use of a physical process which was so far not applied in medicine: electron-positron annihilation. (The process, also referred to as pair annihilation or annihilation, is described in more detail on page 11). Brownell and Sweet surmised that positron detectors would be sufficiently sensitive to depict the brain in high-resolution images. Working with a team of the hospital's medical professionals and physicists, it took them six months to design and construct the first rudimentary, positron emission scanner.

Almost immediately after its completion, the prototype was used to examine patients with suspected brain tumors. During the scan, the patient's head was placed between two opposing sodium iodide detectors which moved back and forth to measure the tracer. The fundamental principle of this construction is still the basis for measuring positrons today: The two detectors work in harmony to measure the pair of photons that move away from each other in opposite directions after an annihilation event. This means that an imaginary line connects the detectors along the path of the photons. The technical term for this path is the *coincidence line* or *line of response*. The clinical image is generated by computing a large number of these lines.

The results from this first prototype were a huge success. "Despite the relative crude nature of this imaging instrument, the brain images were markedly better than those obtained by other imaging devices," writes Brownell in a later report. The team developed a further, in some respects significantly improved, scanner. It was the first device sensitive enough to identify whether a tumor was located in the right or left cerebral hemisphere. Sweet published the results in 1951 in a study on tumor localization. The same year, a group of scientists – among them Philip Handler, who later became president of the American Academy of Science – independently published similar studies in the scientific journal *Science*. These two studies were the point of departure for positron emission measurement in medicine.

Initially, however, not much happened with this new method. In the 1950s and 1960s, Brownell and his team developed a number of improved models, the most advanced of which was used in brain tumor diagnostics for almost a decade. Over the years more and more scientists and investors became involved in the development of this new technique. Two further discoveries from this period had a significant impact on the future of molecular imaging: a series of initial experiments using tomography in nuclear medicine conducted by David Kuhl and Roy Edwards (described on page 25), and the first CT scanner developed by Godfrey Hounsfield (for a detailed history, see page 28). Other noteworthy contributions include Terry Jones's work on developing a method for using positron tracers to measure the oxygen consumption of the brain, and the engineering achievements of David Chesler, who advanced tomography with the addition of *filtered back projection*, which makes it possible to compute an image with low processing power.

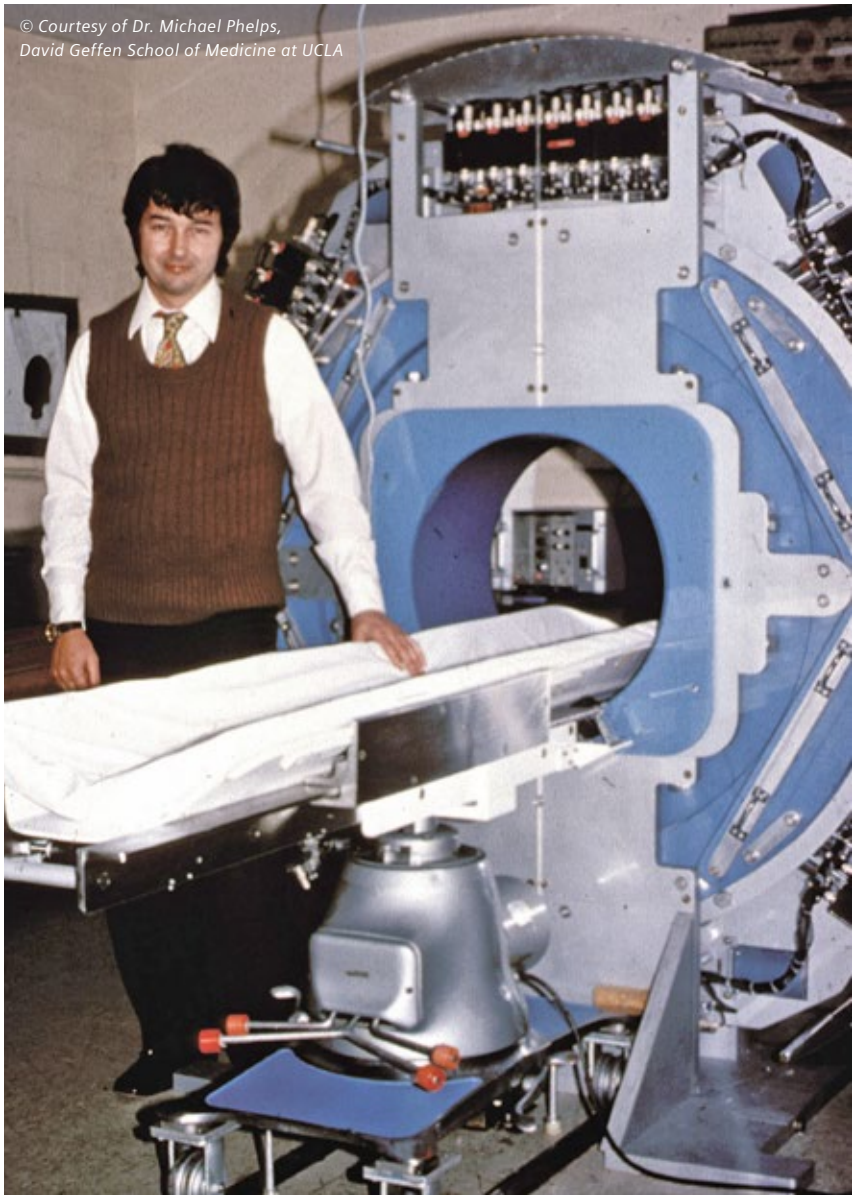
Gordon L. Brownell (l.) with the first clinical positron imaging device, 1953

The first step is always the hardest

All these fundamental studies were still based on the gamma camera principle. Even Chesler acquired his images using two positron cameras that were developed by Brownell's team and, much like today's SPECT, rotated around the patient. The first scanners to use a detector ring – the system architecture still used today – were built by James Robertson at Brookhaven National Laboratory in 1973. The scanner was comprised of 32 detector elements arranged in a ring formation, but did not yet have sufficiently powerful hardware and software to compute images. In the same year, Washington University mathematician and chemist Michael E. Phelps built a scanner that would play a key role in the further development of positron emission tomography.

The device, which Phelps named PETT I, was at first unable to generate any cross-sectional images suitable for clinical practice as it was limited by several technical constraints. For instance, the PETT I used collimators that were of mediocre quality. However, for many of the other cornerstones of the system architecture, Phelps's early prototype played a crucial role and laid the foundations for modern PET. But why did Phelps call his invention PETT I instead of PET I? The acronym PETT stands for "positron emission transaxial tomography". The term "transaxial" describes the image orientation of the system, which roughly translates to "perpendicular to the long axis of the body", and the doctor views the images of the patient from below. In a spinal column image, for example, the doctor's perspective would be from the direction of the hip upwards. Nowadays, the term is rarely used in medicine and in tomography, people refer to images in the transverse plane. Even Phelps later removed the word "transaxial" from the name of his system, as it was not long before images could also be computed from other directions. As a result of his achievements, Phelps is known in expert circles as "the father of PET".

Phelps is not alone in his pioneering work as his colleague and friend, nuclear chemist Edward L. Hoffman, was involved in planning and refining all the prototypes. Phelps and Hoffmann worked together on PET for 39 years, which saw them play a part in almost all the major PET milestones during this period. The first team they created in 1973 included Sung-Cheng Huang, Nizar Mullani, and Michel Ter-Pogossian. In the same year, a second group entered the picture. On their search for technical support, Phelps and Hoffmann travelled from Washington to Oak Ridge, Tennessee, where they presented an advanced model of their PETT scanner to EG&G ORTEC, one of the leading manufacturers of nuclear research instrumentation.



Michael E. Phelps with the PET III

A group of EG&G ORTEC engineers were immediately on board with advancing this promising new technology. Four members of the group were so impressed that, from then on, they dedicated their entire professional lives to PET. They were: Terry D. Douglass, Charles W. Williams, James Kelly Milam, and the vice president of EG&G ORTEC, Ronald Nutt.

Within just a few months, the new team would go on to develop and construct several significantly improved prototypes. During this process, Phelps's original team mainly concentrated on optimizing the physical structure of the scanner, while the EG&G ORTEC group primarily worked on improving the detectors and the analysis electronics. In December 1973, construction of the PETT II began. Just a few months later, in January 1974, the team was able to generate the first test images. All in all, the PETT II can be considered the first fully functional imaging device in the history of modern PET scanners. All subsequent developments furthered the basic principle of the PETT II. Just a few weeks after the construction of this base system, the group built an interim model with a computer-operated table, which Nutt later dubbed the PETT II ½ in his memoirs. This system formed the basis of the findings published by the Phelps team in March 1975 in what is probably the most well-known scientific paper on molecular imaging, *Application of annihilation coincidence detection to transaxial reconstruction tomography*.

In 1974 the next iteration of the PET system was constructed, and was aptly named the PET III. The system was considerably more efficient than the PETT II, partly because it doubled the number of detector elements from 24 to 48. However, the main reason for the historical significance of the PET III was because it generated the first PET whole-body scan of a human being. The published series of images clearly showed a patient's glucose metabolism in the brain. The precision of the images, or rather the accurate depiction of the tracer distribution, was quite unique at the time. The images attracted a great deal of attention in the medical community and undoubtedly represent one of the most important milestones in the history of molecular imaging. However, experts are divided as to when, and with which scanner or event, the PET era actually began. Some authors believe that it all started with the PETT I or the PETT II, while others refer to the PET III and the first brain scan as the catalytic event that led to the birth of modern positron emission tomography.

From the workshop to the lab

Fortunately, consensus on the question of when PET began is rather inconsequential. What is indisputable is that the experience gained from these prototypes led to the first commercial PET scanners. Phelps, Hoffman, Douglass, and Williams received some high-profile support – from David E. Kuhl, the pioneer of molecular imaging – for developing PET III into a marketable product. The team did not hold back on the system's technical equipment. The scanner worked with a PDP-11 16-bit minicomputer, a lavish (for the time) 32-kilobyte RAM, and 96 detector elements. This impressive array of technical equipment came at a price, with the whole system costing almost USD 600,000 (equivalent to around USD 2.7 million in today's money). Then there was the question of what to call the new system. In the end, the team went for a completely new name: ECAT. The acronym stands for *emission computed axial tomography*, and the name was used for all PET scanners in this long-standing series for many years.

ECAT II, the first series-produced PET Scanner, 1978

In December 1976, the first commercial ECAT was installed at the University of California, Los Angeles (UCLA), where Phelps, Hoffman, and Kuhl were employed at the time. One of the works that Hoffmann, Phelps, and Huang published while conducting research at UCLA was a series of papers entitled *Quantitation in positron emission computed tomography*, which is now considered one of the classics of nuclear medicine and is one of the most frequently quoted works in this field. At UCLA, the ECAT was primarily used to investigate glucose metabolism in the brain. However, only six models of this first commercial version were built and sold to various establishments in locations such as Paris and London. The scanner only went into mass production in 1978 with its second version, the ECAT II. All the establishments in the U.S., Japan, and Europe that purchased an ECAT II for research purposes fulfilled one essential prerequisite: they all had access to a piece of equipment which was, at the time, rather unusual – a cyclotron.

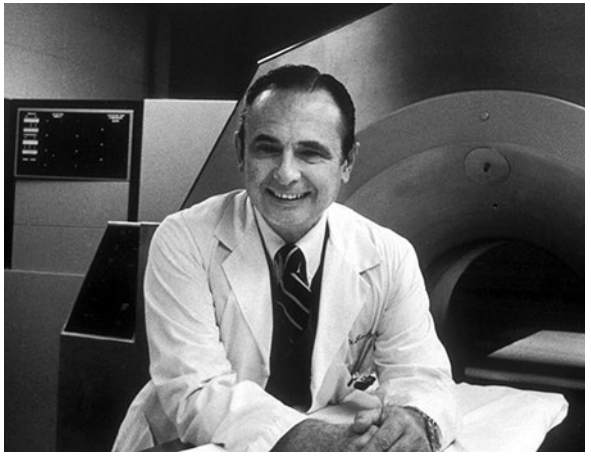
Half-life is of the essence

The cyclotron is an essential component of molecular imaging. Almost all medical radionuclides for PET are produced in this type of particle accelerator. Yet there is a significant difference between SPECT and PET tracers that impacts how they are handled: the half-life of the PET isotope is considerably shorter than that of the SPECT isotope. A PET tracer decays within just a few hours of being produced and has to be manufactured as close as possible to the patient. Particularly in the early years of PET scans, this race against the clock required considerable effort. Either the PET centers had to be equipped with a massive cyclotron weighing several tons, or the tracer had to be flown in by helicopter. The tracers used in the research conducted at the University of Pennsylvania in the 1970s, for example, were brought in by air from Brookhaven National Laboratory, 350 kilometers away.

For his research at Washington University, Michel Ter-Pogossian had access to the cyclotron in the Physics department. As early as the 1960s, this self-confessed "research junkie" started his search for radionuclides that would make it possible to visualize metabolism in the brain. Ter-Pogossian's first major achievement was producing the oxygen-15 isotope using Washington University's cyclotron. The research he conducted over the following years made a significant contribution to the development of almost all PET tracers used today. As a member of Phelps' team in the 1970s, Ter-Pogossian also worked on the first studies with F-18 fluordeoxyglucose, the most widely used tracer in PET scans today. Although Ter-Pogossian was not directly involved in the technical development of the medical cyclotron, he always strongly supported it, so we can assume that he was very happy when the first optimized facilities opened at the end of the 1960s.

But what exactly is the difference between a conventional cyclotron and one optimized for medical use? The massive cyclotrons used in nuclear research were designed to produce huge amounts of energy, with the largest generating up to 500,000,000 electron volts (500 mega-electron volts, MeV, the unit of energy in atomic, nuclear, and particle physics). However, producing a medical tracer only required a maximum of 30,000,000 electron volts (30 MeV). The classical cyclotron was more powerful than necessary to allow its use in healthcare facilities. A breakthrough for PET would require smaller, low-maintenance systems designed to produce appropriate amounts of energy.

In Berkeley, California, not far from the Lawrence Berkeley National Laboratory where Ernest Lawrence built the very first cyclotron in the early 1930s, The Cyclotron Corporation (TCC) started conducting targeted research on the development of medical cyclotrons in the mid-1960s. One of the first relatively compact systems to be produced was the TCC CS-30, which weighed "just" 22 metric tons.



The self-confessed "research junkie," Michel Ter-Pogossian

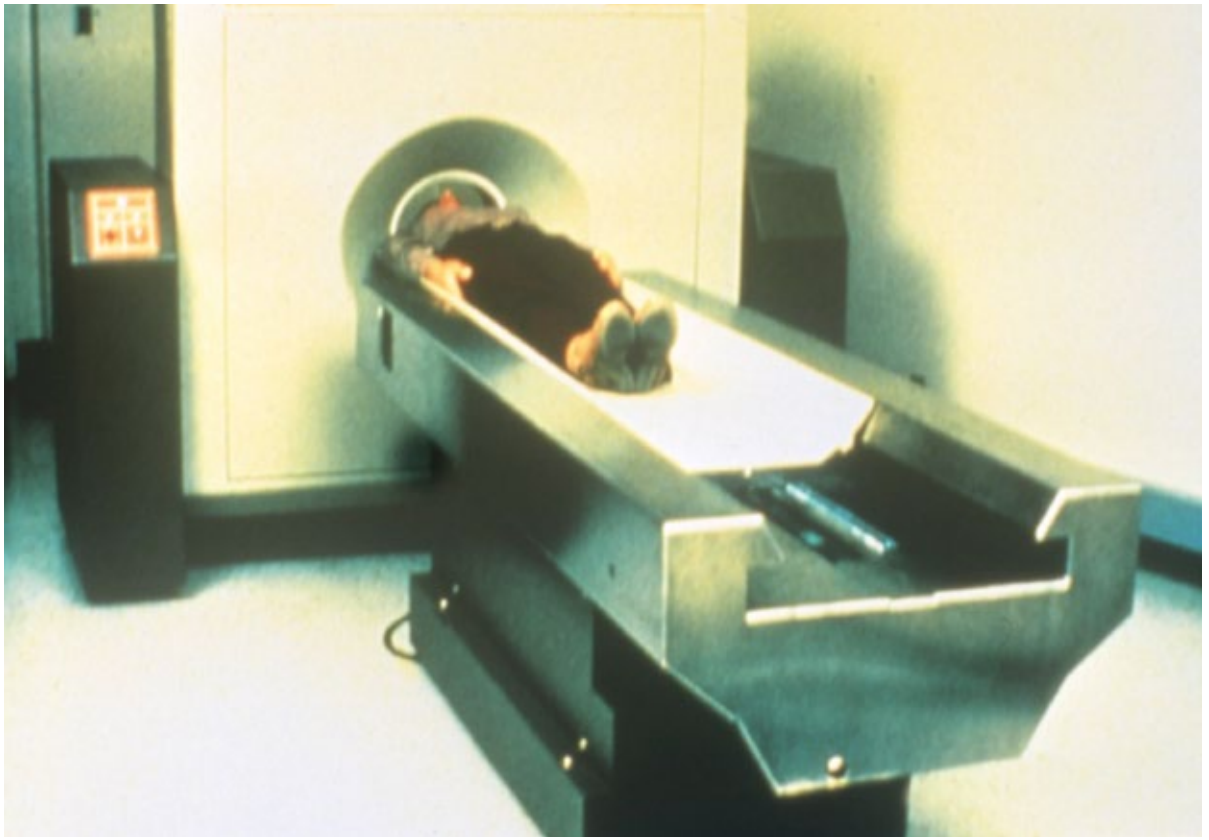
As early as 1970, this cyclotron was routinely used to produce tracers for use in diagnostics and therapy. The development of cyclotrons remained the main focus of The Cyclotron Corporation and the company's engineers went on to contribute major technological advancements. In the late 1970s, TCC also developed a number of PET scanners based on the pioneering work of Gordon L. Brownell; in other words, the scanners comprised two opposing cameras that rotated around the patient's body. The first devices used the tried-and-true sodium iodide as a scintillator. An improved model, which was installed in 1978 at the Memorial Sloan Kettering Cancer Center in New York, used a new material to convert the tracer signals. This new material was bismuth germanate (BGO), an inorganic chemical compound of the elements bismuth and germanium.

Crystal density

The crystal that converts gamma rays emitted from the tracer into light is the bottleneck of every molecular imaging system. The more efficient the scintillator crystal, the more information the system receives about the body, which it can then compute into images. The degree of precision in signal conversion involves a number of factors. The decay time, for example, is the period of time the crystal needs after excitation to be "dark" enough to absorb new information again. Like the gamma cameras in SPECT, the detectors in the first PET systems used sodium iodide crystals. However, the physical properties of the PET tracers placed other demands on the scintillator. Many of the PET tracer signals were not registered in the sodium iodide crystals because the material was not dense enough to efficiently absorb the high-energy photons. With PET scans, a higher-density scintillator has a positive impact on image resolution and brings a whole

gamut of other advantages, such as shortened examination time due to the more rapid measuring of tracer signals. Patients spend less time in "the tube" and doctors can perform more scans per day. The bismuth germanate crystal, known as the BGO detector, was the first scintillator optimized for PET.

All scintillation crystals have specific advantages and disadvantages, and no single crystal is superior to the others in every respect. Sodium iodide, for example, decays much faster than bismuth germanate, but the high density of the elements bismuth and germanium mean that BGO is three times more sensitive. The more sensitive the crystal, the higher the potential image quality of the PET scanner. In 1973, M.J. Weber and R.R. Monchamp discovered that bismuth germanate could convert gamma rays into light. However, it would take a few more years of research for BGO detector technology to be advanced enough for use in a scanner as the manufacturing methods available at the time made it difficult to carry out the complex process of coupling the crystal to the photomultiplier tubes. However, in cooperation with the EG&G ORTEC engineers, Phelps's team did ultimately manage to produce the first commercial PET system using BGO. In 1978, the NeuroECAT, with its 264 BGO elements and photomultipliers, generated images of the human brain that were exceptionally high resolution for the time.



The first PET scanner with BGO elements, the NeuroECAT

Houses and automobiles to secure the future of PET

Thanks to the NeuroECAT images, PET began attracting considerable interest from outside the medical world. This was especially true in March 1981, when an article about PET by Phelps, Kuhn, and colleagues, was published in the academic journal *Science* – with an image of brain metabolism on the cover. By the 1980s, it was obvious that PET was becoming more than a useful tool for medical research. With the aim of putting the processes developed at the university into clinical practice, a small group of EG&G ORTEC engineers established a start-up company in 1983 that was exclusively focused on the development of PET. It was called Computer Technology and Imaging, Inc. (CTI), and was headquartered in Knoxville, Tennessee.

Four of the five founders of CTI were part of the team that built the first functioning PET prototypes ten years earlier: Terry Douglass, Ronald Nutt, James Kelly Milam, and the inventor of PET himself, Michael E. Phelps. The fifth member of the team was EG&G ORTEC's former product manager, Mike Crabtree. The future of PET was still unclear, yet, the five founders of CTI were so deeply convinced of their vision that they combined all their savings and even pledged

their houses and cars to buy the PET business from EG&G ORTEC for just under USD 3 million. In the spring of 1984, CTI hired a further 22 technicians and engineers and set ambitious goals. The plan was, via user-friendly technology and a simplified approach to obtaining tracers, to make PET as valuable and practical a imaging procedure as computed tomography and magnetic resonance imaging.

From research to clinical practice

For PET to make the transition from research to clinical practice, CTI needed to develop an affordable and practical scanner. At the same time, an entire infrastructure was needed to support the PET scan itself. One of the issues was that tracers were produced by a small number of cyclotrons spread around the country, frequently some distance from potential patients. This dilemma could be solved in one of two different ways by either developing small, cost-effective cyclotrons designed for use in hospitals, or by establishing an extremely efficient distribution network to transport the tracers quickly and safely to hospitals that needed them. Shortly after CTI was founded, the opportunity arose for the company to work with TCC on implementing one of these approaches.

In 1983, in the relatively small market for medical particle accelerators, The Cyclotron Corporation ran into financial difficulties and CTI decided to support TCC in manufacturing three different cyclotrons. One of the cyclotrons produced tracers for PET research, and the other two generated radionuclides for nuclear medicine in the treatment of cancer. Over the following year, CTI and TCC deepened their partnership. CTI commissioned a team of TCC staff – led by George O. Hendry, the godson of Ernest O. Lawrence, the inventor of the cyclotron – to develop a user-friendly mini cyclotron. By the end of 1985, CTI completely took over The Cyclotron Corporation and the first mini cyclotron model, christened Radioisotope Delivery System 112 (RDS 112), was installed at the University of Wisconsin School of Medicine and Public Health. This first RDS 112 remains in use at the University of Wisconsin to this day. Since 1985, the device produced hundreds of tracers for patient scans and was used to train students and serve clinicians from around the world. Throughout this period of more than 30 years, the mini cyclotron's downtime (when the device stands idle, for instance due to maintenance work) totals less than one percent. The system architecture of the very first RDS still serves as the basis for the production of modern PET tracers today.

The aim of the second approach was for CTI to create an alternative solution for healthcare facilities that either could not, or did not want to, operate their own cyclotron. From the late 1980s CTI began to establish cyclotron facilities in major metropolitan

Radioisotope Delivery System 112 (RDS 112), photographed in 1989

areas, which produced tracers and delivered them to all PET centers across the region. Over the years, this distribution solution – called PETNET Solutions – evolved into the world's largest supplier of PET radiopharmaceutical products. The combination of these two approaches, the development of the mini-cyclotron and the establishment of the PETNET distribution network, played a major role in PET becoming one of the most important imaging procedure from the mid-1990s.

CTI and Siemens

In 1985, Siemens invested in the young company and helped CTI further develop PET technology. A year later, Siemens took over CTI's global distribution and service for all PET scanners and RDS cyclotrons (with the exception of the U.S.). In 1987, the two companies decided to significantly expand their partnership for the long term: they jointly formed the CTI PET Systems, Inc. (CPS) venture, in which Siemens became the first major enterprise to enter the field of positron emission tomography. From then on, all ECAT systems jointly developed by the two companies would bear the Siemens logo. At the end of the 1980s, PET was still predominantly a research tool. However, everything that a potential PET center would need – a scanner, tracer produced by an in-house cyclotron or supplied via a distribution network, customer service, and consultancy – could, for the first time, be found under one roof. In addition, the technology was making significant advances.

From the mid-1980s, technological development and research into new clinical applications really picked up steam. CTI and Siemens applied fora whole host of patents, which retain their technical importance to this day. The major milestones of this period include the block detector, the depiction of heart metabolism in images of unprecedented quality, and the first three-dimensional images of the whole body. The block detector, developed by Ronald Nutt and Mike Casey, circumvents a physical limitation of the conventional design. Until 1985, each crystal in the detector ring had to be coupled with a photo-multiplier. To improve image resolution, the number of these components had to increase in pairs. As well as being costly, this also involved a very laborious manufacturing process. Nutt and Casey developed a method where multiple crystals share one photomultiplier and this development laid the foundation for today's high-resolution PET scanners. Virtually all systems manufactured since 1985 are based on block detector technology.

Wholeheartedly, and from head to toe

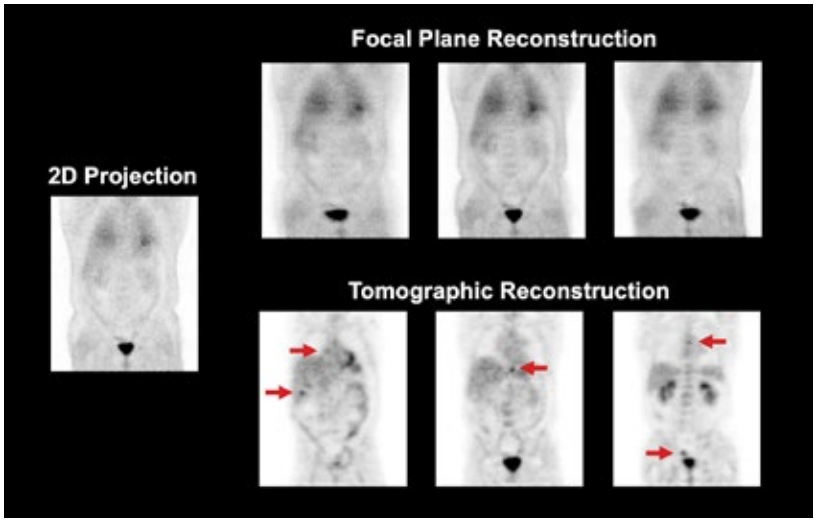
Once again, Michael E. Phelps was one of the leading figures behind the development of another major milestone during this period. Imaging the heart was always one of the biggest challenges in the development of medical technology. Every single minute, the human heart pumps approximately five liters of blood around the body's circulatory system, which is almost the entire volume of blood in the average adult human. The rapid contraction of the muscle and its fine tissue structures, with their extensive branching, place particular demands on imaging. Over the years, Siemens developed or improved many cardiac-imaging procedures, all of which have their own particular strengths. Ultrasound, for example, enables clinicians to quickly and accurately examine the function of the heart valves, while computed tomography can visualize the coronary vessels and arteries down to the finest offshoots. Yet PET depicts the heart's metabolism with more precision than any other procedure. The first successful PET image of the heart was acquired in 1985 when Phelps, Heinrich Schelbert, Markus Schwaiger, and their team at the University of

From the late-1980s, ECAT systems would bear the Siemens logo.

California, Los Angeles (UCLA), visualized the blood flow and the oxygen metabolism of the heart muscle. From then on, the diagnosis of heart conditions was the focus of clinical PET for many years, and to this day cardiac imaging – along with cancer diagnostics – remains one of PET's main strengths. The essential prerequisite for tumor screening is the ability to depict large parts of the body, or the whole body, three dimensionally using a PET scan.

The 1980s saw the publication of a gamut of studies on tumor diagnostics using PET. From the middle of the decade, it was safe to say that the degree of malignancy of a brain tumor was directly propor-tional to the tumor's F-18 fluordeoxyglucose (FDG) uptake. PET made it possible to determine the exact volume of FDG being absorbed by the tumor. At the time, however, PET could only be used to visualize individual regions of the body or organs, which made it virtually unusable for diagnostics and therapy monitoring in cancer treatment. Depicting the patient's entire body required multiple individual scans that were then combined to generate an image. Patients could hardly be expected to undergo so many examinations, as well as all the preparation each one involved. The whole-body scan developed by Phelps, Hoffman, and colleagues in 1990 instan-taneously made PET an excellent tool for detecting tumors and metastases.

On the surface, the main difference between this new method and conventional methods was quite simple: up until that point, the patient would lie on a table fixed in position in the gantry while the scanner mapped the distribution of the tracer in a confined region of the body. With the whole-body scan, however, patients lay on a table that moved them a few centimeters into the gantry. For around five to ten minutes, the system recorded the tracer distribution in the measurement field before moving the patient to the next section. These steps were repeated between eight and twelve times, depending on the size of the patient. To facilitate this rather tricky way of recording measurements, Phelps's team developed more complex mathematical algorithms to reconstruct the final image from the data collected in this step-wise fashion. In early 1991, one year after starting development of the new method, the team published the results from the first whole-body scan for oncological purposes. This sparked a whole series of PET studies, mainly focused on differentiating between benign and malignant tumors. Today's nuclear medicine and molecular imaging specialists consider the development of the whole-body scan to be one of the most important advancements in the history of PET. The next major milestone in the development of PET was a combination of two techniques that would prove to be one of the most significant imaging procedures in modern medicine.



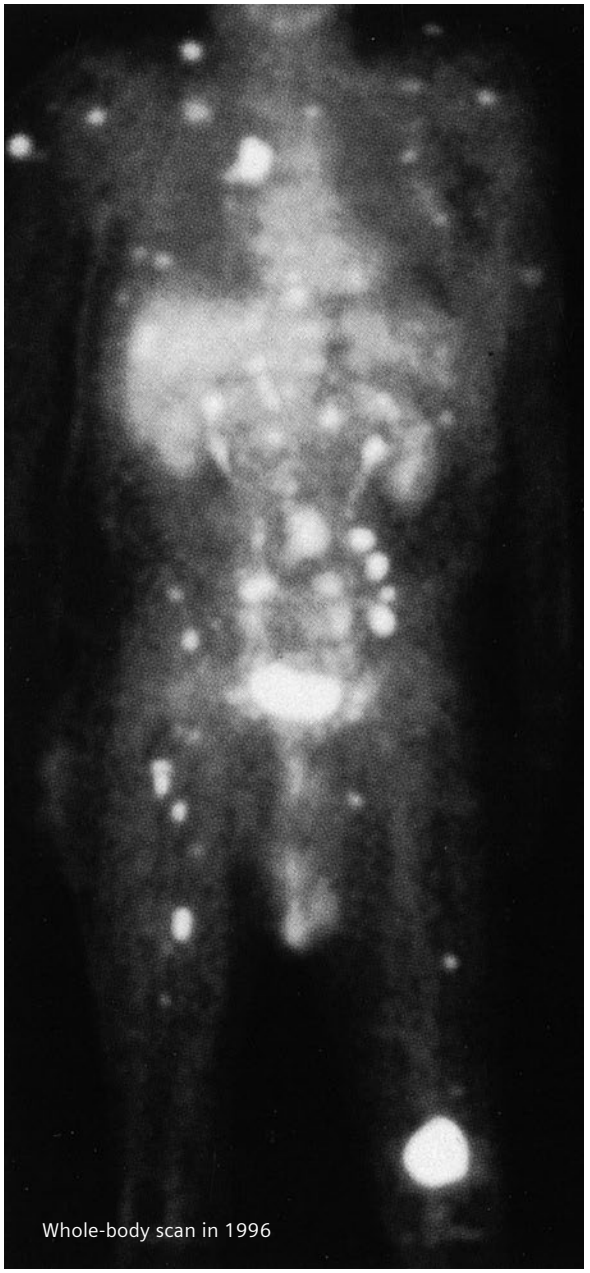
First whole-body PET Images in oncology, 1989

© Courtesy of Magnus Dahlbom, Edward Hoffman, Michael Phelps, David Geffen School of Medicine at UCLA

The time is now

The joint venture between CTI and Siemens converted the developments achieved in the late 1980s and early 1990s into clinical systems. Thanks to the large number of major technological advances at the time, substantially improved models were released almost every year, sometimes even twice a year. The PET Center, for example, established under the CTI name in 1985, was offered as a complete package that included a mini cyclotron. The same year, the ECAT 931 entered the market. Its block detector technology significantly improved PET resolution. From 1989, the Siemens ECAT 953b enabled acquisition of three-dimen-sional images and also measured tracer signals four times more efficiently than its predecessors. The Siemens ECAT EXACT made it possible to use whole-body scans in clinical practice from 1991, the same year that the technique was invented. The successor model, the ECAT EXACT HR, improved the resolution from the conventional ten millimeters to less than four millimeters. The ECAT EXACT models represented such a major technological leap forward that, in the 1990s, they

The ECAT EXACT models in the 1990s became the most widely used PET system family in the world



Whole-body scan in 1996

became the most widely used PET system family in the world. An equally important contribution to the establishment of PET was the development of the entry-level Siemens ECAT ART, which was optimized for use in smaller practices and hospitals. Now, with these detailed images of heart metabolism and the ability to perform whole-body scans, the real breakthrough began for PET. In the April 1991 edition of the *Journal of Nuclear Medicine*, in which Phelps and his colleagues presented their latest advances, the teaser on the cover read, "Clinical PET: It's Time Has Come." In the years that followed, a plethora of studies conducted in hospitals and universities demonstrated the huge benefits of the procedure in the early diagnosis of many different diseases. During the 1990s, numerous investigations provided evidence that FDG was ideal for monitoring chemotherapy response. Thanks to the broad acceptance of the research findings, health insurance companies began covering the costs of PET scans that used FDG.

Rare and exorbitantly expensive

There is no such thing as a perfect crystal. This is something physicist Charles L. Melcher explored in a paper on scintillation for PET. The crystal that Melcher discovered in the early 1990s, and bears the rather cumbersome name of *lutetium oxyorthosilicate*, is close to perfect. Lutetium oxyorthosilicate, or LSO, is a compound made up of the elements lutetium, silicon, and oxygen. In terms of density, the crystal's structure is similar to BGO, but it shines considerably brighter when photons from the tracer collide with the crystal. Moreover, LSO can absorb new signals quickly as its decay time is far shorter than that of BGO crystals. Expressed in numerical terms, the LSO crystal generates five times more light in the scintillator and can absorb more gamma rays after just 40 nanoseconds, while BGO needs a full 300 nanoseconds to decay. In sum, LSO is around 37.5 times more efficient than BGO. This reduces the amount of tracer with which a patient is injected and shortens the scan time by up to ten minutes. The high efficiency of the crystal makes the entire PET scanner more effective, and even makes it possible to use new examination procedures. In a time-of-flight scan, one of the most informative contemporary PET examination procedures, the system measures the miniscule time difference between the collision of each of the two photons with the opposite side of the detector ring. The system can use this to approximate the location of the positron annihilation, which in turn enables it to produce high resolution images. BGO is far too slow for time-of-flight scans.

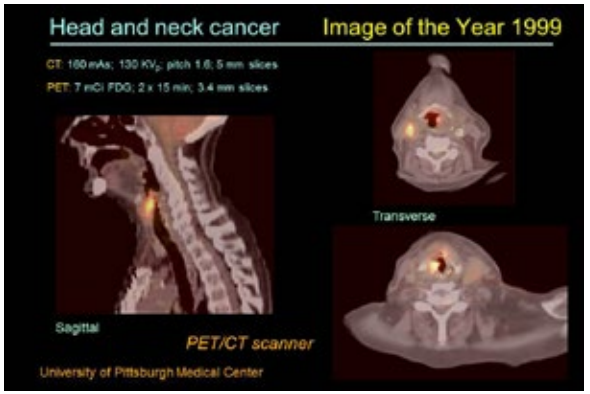
In the mid-1990s, however, it did not seem as though LSO was going to be the scintillator of the future. Lutetium is one of the rarest of the rare earth metals. All the elements in this group are extremely difficult to extract, but the extraction of lutetium is particularly laborious and expensive. At the time, just a few grams were available, and PET was the only potential commercial use. Nevertheless, CTI PET Systems decided to use lutetium as a PET detector. In 1996 Melcher joined CTI, where he headed the development of LSO from the research stage to the first serial production of LSO detectors. Over the years that followed, LSO production was refined and made substantially cheaper, in part thanks to the partnership between CTI engineer Mark Andreaco and University of Tennessee chemist George Schweitzer. In 1998, an image generated by an LSO detector prototype was awarded the Image of the Year accolade by the Society of Nuclear Medicine. From 1999, CTI PET Systems was able to produce LSO in larger quantities and at a price that was only marginally higher than BGO.

By the turn of the millennium, CTI PET Systems had brought the first series-produced systems equipped with LSO detectors onto the market: the Siemens ECAT Accel™ whole-body scanner, and the Siemens ECAT HRRT™ brain scanner that was developed in cooperation with the Max Planck Institute for Neurological Research in Cologne. The ECAT HRRT was the first PET system able to visualize the metabolism in the brain with a resolution of 2.5 millimeters. The system used around six times more crystals than six years previously as the 1993 ECAT EXACT used 18,816 BGO crystals to measure the distribution of tracer, while the ECAT HRRT worked with 119,808 LSO crystals.

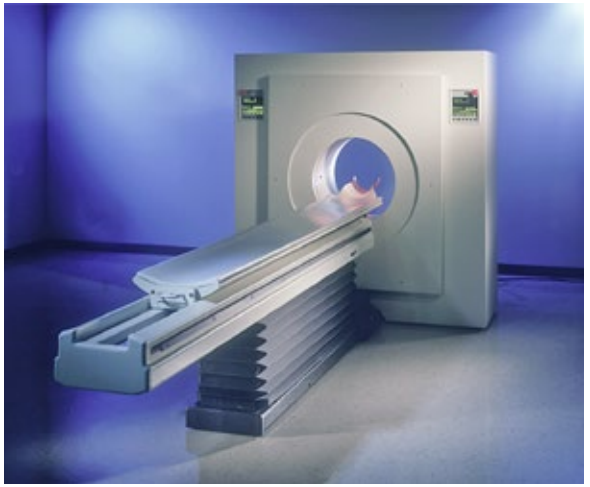
The discovery of the year 2000

Around 25 years after Phelps designed his first prototype, PET had become one of the most important imaging procedures in medicine. Doctors were able to monitor their patients' metabolism using detailed images, and could frequently identify disorders even before they affected their patients' body tissue. However, non-emitting body tissue is not visible on scan images and, in terms of depicting anatomy, this is PET's Achilles heel. For many examinations, doctors need to know precisely where in the body the metabolic processes are taking place. During the 1980s, clinicians often compared two separate scans, one acquired with a PET scanner and one with a CT, to pinpoint the location of the metabolic processes as precisely as possible. From the 1990s, software algorithms could superimpose two different scans to simultaneously depict metabolic processes and anatomical structures in one image. For visualizing relatively immobile organs such as the brain, this method, known as image fusion, was considerably more accurate than a visual comparison of two images. However, virtually all other regions of the body are in constant motion. Each breath a person

The first PET Scanner with LSO crystals, the ECAT Accel, 2000



One of the first PET/CT scans, awarded Image of the Year 1999 by SNM



ECAT ART, the PET component for the first PET/CT

takes moves the body's organs in back and forth, for example. Particularly if a patient was repositioned for two different examinations in two different scanners (which often even involved moving to another hospital department), this could cause body tissue to shift by several millimeters or even centimeters. The ability to simultaneously acquire PET and CT images would therefore benefit molecular imaging tremendously.

The first known hybrid system combined PET and CT in what today would be considered a rather unusual manner – not together in one device, but rather via a transportation system located in one room. In 1984, at Japan's Gunma University, the Japanese professor Teruo Nagai built a facility where a PET and CT scanner were positioned side by side. The examination table could move from one scanner to the other on a platform positioned parallel to a gantry so the patient did not have to move. Completely unaware of this facility, Ronald Nutt and the particle physicist David W. Townsend, from the University of Pittsburgh, devised a system that combined PET and CT in one gantry. They applied for a patent on the concept and began preparing to build a prototype.

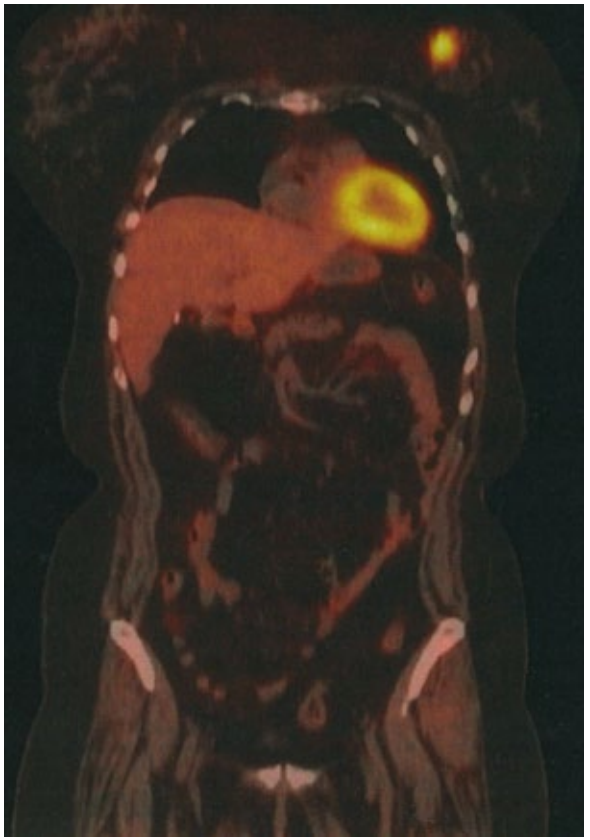
In 1998 a collaboration between CTI PET Systems and the Siemens CT development unit in Forchheim began, and along with support from the National Cancer Institute. The development of the first contemporary combined PET/CT scanner took place at the University of Pittsburgh. Thomas Beyer, then a research associate at the university, built a prototype by combining the SOMATOM AR CT scanner from Forchheim with an ECAT ART PET scanner from Knoxville to create a system named the SMART scanner. The first scans, performed on more than 300 oncology patients, demonstrated the enormous potential of PET/CT in oncology. The Society of Nuclear Medicine (SNM) awarded one of these images, the title of Image of the Year 1999. CTI and Siemens decided to optimize this combined system for clinical use and prepare it for commercial production. The CT team, led by Siemens system engineer Andres Sommer, was tasked with finding the best possible components and synchronizing them.

Sommer's team developed a special version of the Siemens SOMATOM Emotion, which was one of the most compact CT scanners at that time. "We shipped the scanner to Knoxville and put it into operation there," Sommer recalls around 20 years later. Something that sounds so simple was to become one of the most important discoveries in the history of Siemens Healthineers. In the year 2000, the system was unveiled at the Society of Nuclear Medicine Annual Congress under the name of Biograph. *Time* magazine awarded it the title of Medical Invention of the Year 2000, and numerous hospitals including UCLA, the Memorial Sloan Kettering Cancer Center in New York, and Essen University Hospital in Germany, integrated the system into their clinical practice immediately after series production began. Apart from the work of David W. Townsend, the rapid breakthrough of PET/CT was largely thanks to the tireless efforts of Ronald Nutt. In a way, Nutt, who was president of CTI PET Systems at the time, formed a bridge between the PET engineers in Knoxville and the CT developers in Forchheim. In the early 2000s, Siemens established a research department within the CT development unit in Forchheim. This department collaborated seamlessly with the team in Knoxville on the ongoing development of PET/CT.

The first commercial PET/CT
from Siemens, Biograph, 2011

One of the ten greatest medical discoveries of the millennium

Around the year 2000, PET increasingly began to make headlines outside expert circles. Numerous newspapers and magazines ran reports on this latest development in contemporary imaging.



High-resolution image acquired with Biograph Sensation 16

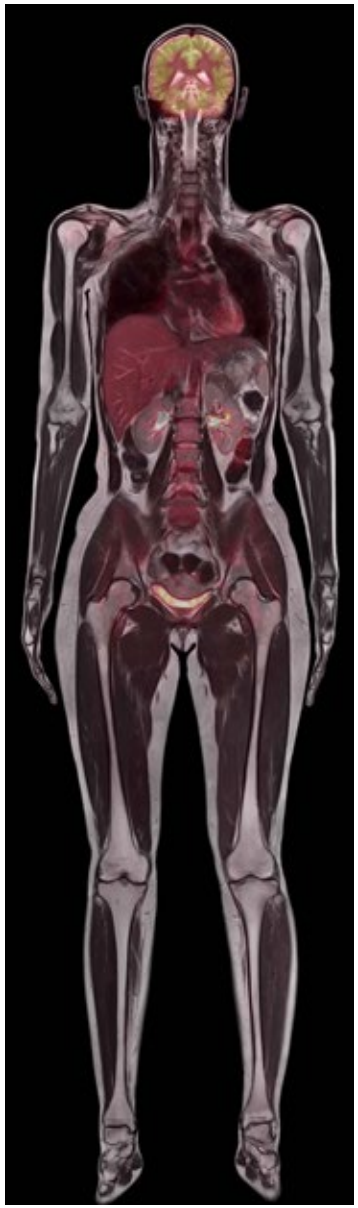
On October 4, 1999, one of the largest daily newspapers in the U.S., the *Dallas Morning News*, even referred to PET as one of the ten greatest discoveries of the millennium, on a par with the Gregorian calendar, the mechanical clock, the steam engine, and the Internet. Combining PET with CT increased its value to both research and clinical practice. From 2002, PET/CT was one of the fastest growing imaging techniques in the history of medical technology. Major hospitals and healthcare facilities replaced their PET scanners with PET/CT hybrid systems. In 2006, standalone PET systems were taken off the market.

In the first half of the 2000s, CTI PET Systems worked with Siemens engineers in Erlangen to optimize the *syngo*® software for PET/CT, and with the team in Forchheim to develop significantly more efficient models. The Siemens Biograph Sensation 16, for instance, was launched in 2002 and could perform a high-resolution, head-to-toe scan of a patient in just a few minutes. The first Biograph needed between 30 and 45 minutes for a whole-body scan. While working on these developments, the collaborative partnership between CTI and Siemens became closer and in June 2005 everyone was brought together under one roof. Siemens took over CTI Molecular Imaging, along with all its subsidiaries including the cyclotron development unit and PETNET Solutions. With this expansion, the Siemens Nuclear Medicine business division, headquartered in Hoffman Estates, was renamed Siemens Molecular Imaging. For Siemens, this official merger signified a major milestone in the company's history, as it meant that all key imaging procedures and supporting infrastructure were now incorporated into one company. In the words of Erich Reinhardt, then CEO of Siemens Medical Solutions: "This step is a natural continuation of our long-standing partnership with CTI and reflects Siemens' overarching strategy to improve the efficiency of the healthcare system."

The "impossible" invention

One of the key contemporary imaging procedures under the umbrella of Siemens Healthineers is magnetic resonance imaging, often shortened to MR or MRI. One of the most important features of this technology is its ability to depict soft tissue such as the liver, the joints, the heart muscle, and the brain in unparalleled detail. In simple terms, MR utilizes the magnetic properties of the body by aligning the hydrogen atoms of body tissue in a magnetic field and converting the information into images. This magnetic field is what hampered the development of a hybrid PET/MR system for so long. The PET photomultipliers are so sensitive that they have to be shielded from the Earth's relatively weak magnetic field. Conventional PET detectors therefore cannot function without interference even in the vicinity of an MRI scanner – let alone in the same casing. The solution to this physical problem lies in semi-conductor technology.

The 1990s saw the start of the complex process of developing semiconductor detectors capable of converting light from the PET crystal into electrical signals without interference. Initially, these converters were used in a kind of mini PET/MR, in what were referred to as preclinical systems, used to conduct research into the metabolism of small animals. The first detector ring big enough to scan a human brain was built by Siemens Molecular Imaging in 2006. The special semiconductor detector was far from ready for series production but was already being used in an MR system with a magnetic flux density of three Tesla, which is about 60,000 times stronger than the Earth's magnetic field. After another four years of development, financed by the DFG research funding organization, Siemens unveiled the world's first PET/MR system capable of visualizing the entire human body using both techniques at the same time, Biograph mMR.



A whole-body scan taken
with Biograph mMR in 2010

Scan preparation with
Biograph mMR, 2011

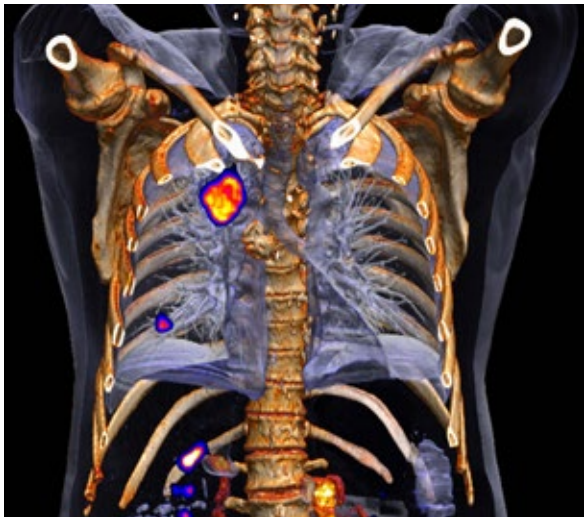
The first clinical application test of Biograph mMR (mMR stands for molecular magnetic resonance) started on November 19 in the Department of Nuclear Medicine at the Rechts der Isar Hospital, which is part of the Technical University of Munich, in Germany. The director of the department at the time was Markus Schwaiger, a pioneer of PET cardiac imaging who had worked closely with Michael E. Phelps and colleagues in 1985 to produce the first successful PET images of the heart. The aim was for the PET/MR in Munich to be used for applications such as therapy planning and in the long after-care process for cancer patients. The particular strengths of Biograph mMR included its ability to produce detailed images of the nervous system, which can help precisely identify affected tissue when screening for conditions such as dementia or epilepsy. In contemporary clinical practice, PET/MR is well suited to help assess how a patient's body might respond to medication, for instance. Biograph mMR can also help in a research context by supporting the development of new tracers and therapies.

Everything flows

With the next generation of the Biograph family, Siemens introduced a whole range of new technologies which Siemens Healthineers still uses in its systems today, including the high-definition PET detectors, improved reconstruction algorithms like ultraHD-PET and *SAFIRE* software, which made it possible to reduce the radiation dose by up to 60 percent while still maintaining the same image quality. The scan was now a far more comfortable experience for patients than before. The bore diameter in the 2008 Biograph mCT™ was 78 centi-meters (compared to the previous 70 centimeters), the gantry was much shorter than in the older systems, and the patient table could bear a load of up to 227 kilos. Patients also benefited from the groundbreaking technology that powered the 2013 Biograph mCT Flow™, and the image quality benefited even more. Up until 2013, PET images were created using the stop-and-go method which experts also referred to, slightly tongue-in-cheek, as the step-and-shoot method. For the procedure, the table moved the patient a couple of centimeters into the gantry and paused for several minutes until a few centimeters of the patient had been scanned. All this was then repeated until the image was complete. The Biograph mCT Flow was the first system to move the patient table through the gantry continuously on a magnetic track. However, the technology for this couldn't simply be integrated into a conventional system. Virtually all the components – the table, the detectors, the algorithm used to compute the image – was redeveloped specifically for this FlowMotion™ technology, which was the first of its kind anywhere in the world.

Images instead of guesswork

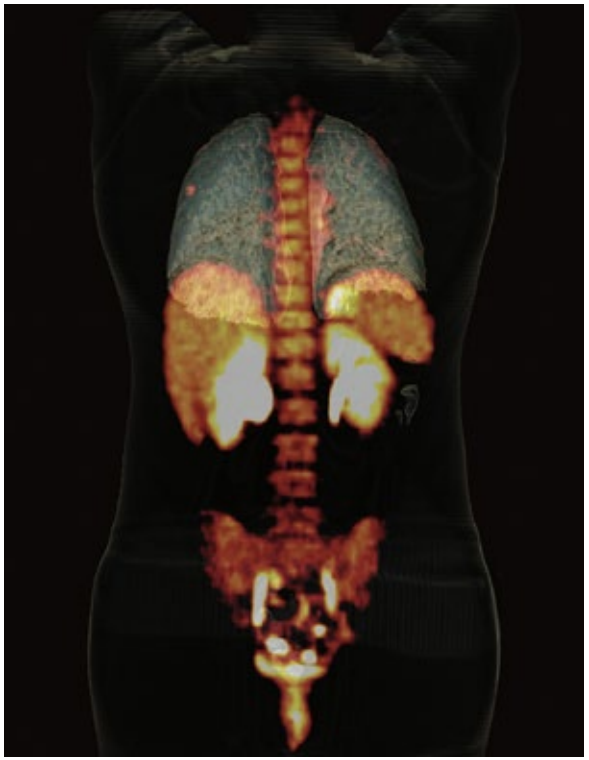
The treatment of cancerous tumors using electromagnetic waves is one of the oldest applications of X-ray technology. In 1896, just a couple of months after Röntgen's discovery, clinicians discovered that X-rays could help treat tumor diseases. Particularly in these first decades of what was referred to as radiation oncology, or radiotherapeutics, the imprecise imaging hampered pre-radiation preparation. With the methods available at the time, clinicians could usually only estimate where the tumor stopped and healthy tissue began. This made it virtually impossible to accurately target a tumor with radiation while preserving the surrounding healthy tissue. In the 1970s and 1980s, CT and MR imaging represented a huge step forward: later combining these methods with PET was at least an equally large step forward for therapy planning.



Upper body scan with Biograph mCT Flow in 2013

The current model of the Siemens Healthineers Biograph mCT

Biograph Horizon, introduced in 2015



Clinical image acquired on Biograph Horizon in 2015

In many hospitals, one of the main uses of PET/CT is for planning cancer therapies. To further optimize this application, Siemens developed its Biograph RT edition, an extension that can enhance any PET/CT scanner in the Biograph family. The Biograph RT edition (RT is short for radiation therapy) includes special algorithms to depict body contours and iMAR (iterative metal artifact reduction) software to reduce the image interference caused by metal objects such as hip implants, prosthetic shoulders, and dental fillings. *syngo* software is enhanced with specialized applications such as *syngo*.PET&CT Therapy, which are designed to facilitate collaboration between radiologists, experts in nuclear medicine, and oncologists, by allowing the radiologist to highlight the precise target area for the oncologist.

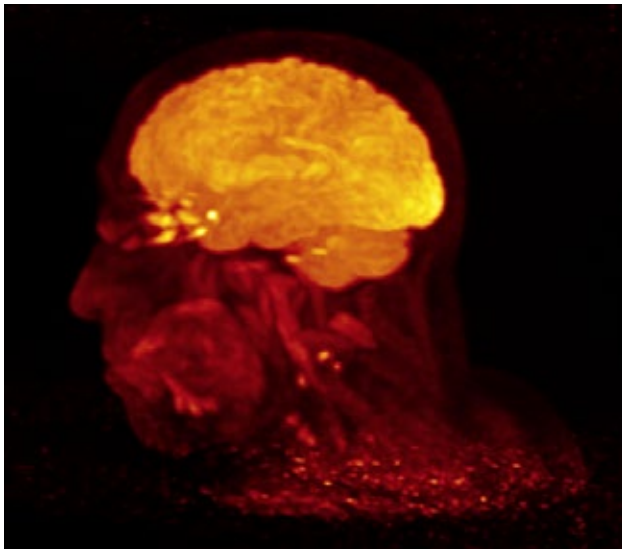
Barriers to entry for PET/CT are still higher than for standalone CT systems or for SPECT/CT hybrids. For smaller practices and hospitals, space for the system is often lacking, the operating costs are too high, or the maintenance is too laborious. Biograph Horizon was designed for practices with these limitations in mind, with the goal of being an approachable PET/CT solution. When the system was launched in 2015, it was the smallest PET/CT scanner with the lowest power consumption. All commercially available PET tracers can be used. The entrance level scanner is equipped with LSO crystals and allows time-of-flight scans, so routine scans can be performed in down to five minutes. From 2016, the Biograph Horizon Flow edition was even available with optional FlowMotion technology.

Vision for the future

During the pioneering age of PET, now almost 45 years ago, the development team comprised just a small group of engineers. Phelps, Hoffman, Nutt, and their colleagues designed and constructed new scanners in an astonishingly short period of time, and sometimes managed to bring these systems to the market within just a few months. Over the years – due to increasingly complex microelectronics, multifaceted system architecture, and the elaborate process of software development – these teams of developers steadily expanded. Today, when Siemens Healthineers develops a system, it engages a network of dozens, if not hundreds, of engineers from around the world. Just developing the system architecture for the high-end scanner, Biograph Vision™, involved over 200 members of staff. When building a modern scanner, one of the team's most important tasks is to coordinate the components so the entire system is as efficient as the individual parts permit. To do this, the team tests various configurations and builds prototypes to compare the setups in practice. One of the scientists, Melika Roknsharifi, recalls during the development phase of the Biograph Vision, even the first test systems produced impressive images: "This was still just the first prototype, and we were all confident that the final version would be even better." In collaboration with Centre Hospitalier Universitaire Vaudois (CHUV) in Switzerland and the University Medical Center Groningen (UMCG) in the Netherlands, the Knoxville team built, tested, and modified more prototypes. After more than 2,500 different versions, they found the optimum configuration.

The reason the process was so cumbersome was that many components had to be redeveloped from scratch. The Optiso Ultra Dynamic Range (UDR) detector technology, for instance, was no longer based on conventional photomultipliers but rather on silicon photomultipliers (SiPMs), which built on the technology that powered the Biograph mMR. The tiny LSO crystals were now so sensitive they could record time differences down to 0.000 000 000 214 seconds between two corresponding detector events. This made time-of-flight imaging the fastest of any PET/CT scanner available at the time. "The Biograph Vision PET/CT system makes a significant leap in performance beyond anything we have ever built," said Jim Williams, then head of Siemens Healthineers Molecular Imaging. The scanner was unveiled at the 30th Annual Congress of the European Association of Nuclear Medicine (EANM) in Vienna in 2017. The product launch was one of the most important mile-stones in the history of Siemens' medical technology development for two main reasons: Biograph Vision was both the first in a new generation of systems and the first PET/CT scanner to enter the market under the new Siemens Healthineers brand.

The Biograph Vision team



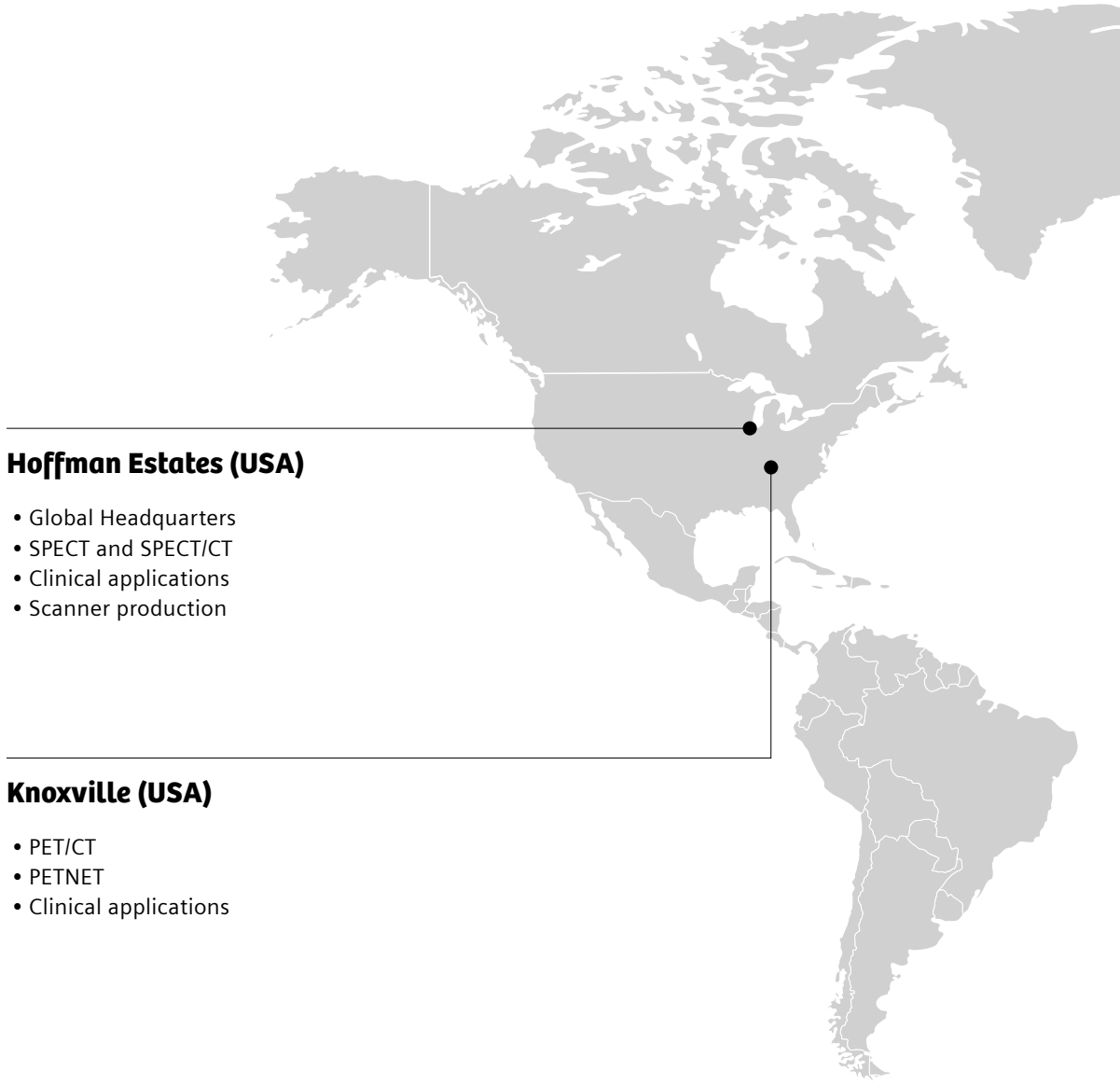
Brain image taken with Biograph Vision

The next generation of
PET Scanners, Biograph Vision

Common features

125 years after the discovery of radioactivity, molecular imaging is one of the most useful imaging procedures in medicine. Thousands of individuals – clinicians, engineers, physicists, biologists, and many other experts – all played a part in this development: from the decades of research during the first half of the 20th century, to the pioneering work of inventors like George de Hevesy, Hal O. Anger, and Michael E. Phelps; to the optimism of entrepreneurs such as John Kuranz and Ronald Nutt; to today's expansive teams of multi-disciplinary professionals.

Today, Siemens Healthineers can look back over 60 years of experience in molecular imaging. During this time, the company succeeded in consolidating the entire supporting infrastructure under one roof. Siemens Healthineers manufactures collimators and detectors in-house, the scintillators grow in the company's own crystal factory, and PETNET Solutions supplies over 2,800 imaging centers worldwide with hundreds of thousands of tracers every year. The SPECT and PET/CT scanners from Hoffman Estates and Knoxville perform around 13 million scans for diagnostic purposes or therapy monitoring each year, and the anticipation is that this figure will continue to rise in the coming years. Molecular imaging has the potential to make significant contributions to the increasingly important field of precision medicine.



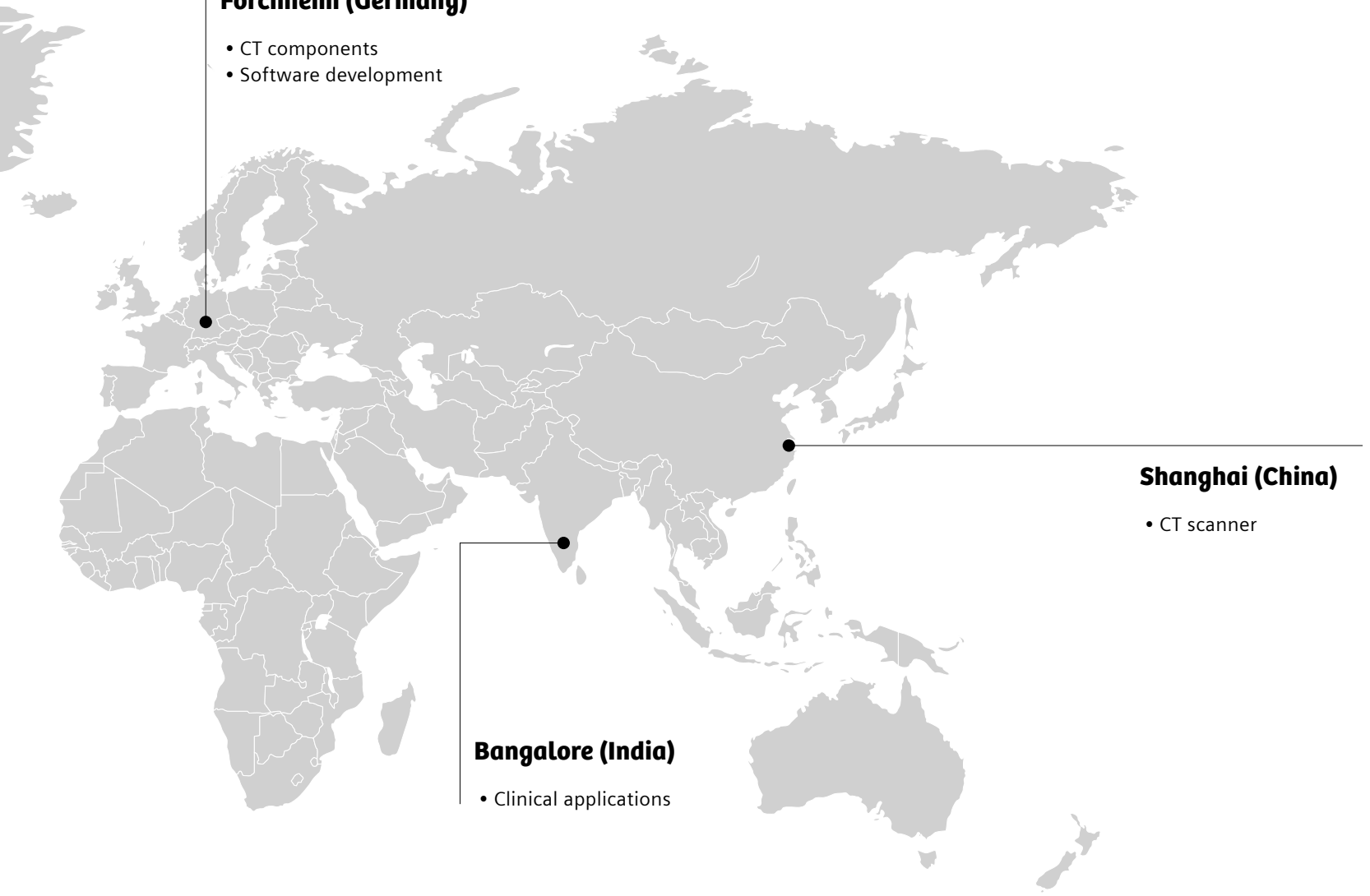
Hoffman Estates (USA)

- Global Headquarters
- SPECT and SPECT/CT
- Clinical applications
- Scanner production

Knoxville (USA)

- PET/CT
- PETNET
- Clinical applications

Locations of Siemens Healthineers Molecular Imaging – A global network of innovation



Forchheim (Germany)

- CT components
- Software development

Shanghai (China)

- CT scanner

Bangalore (India)

- Clinical applications

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