Nuclear Medicine

Radioactivity for Diagnosis and Therapy

2nd edition

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edp sciences

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To Christiane

This work is dedicated to all the anonymous persons who are directly or indirectly involved in the discovery, development, preparation, handling and application of radiodiagnostics and radiotherapeutics. They are technicians, cyclotronists, engineers, radiochemists, radiopharmacists, biologists, clinicians, nurses, scientists, salesmen, specialists of radioprotection and safety, experts in quality and logistics, environment professionals, regulatory affairs authorities, maintenance specialists, archivists, etc., Without their precious contribution, nuclear physicians and radiotherapists would not be able to bring to their patients – who are often affected by extremely invalidating diseases, sometimes considered as incurable – the benefit of these extremely complex and particularly efficient products.

Hence, this work is also dedicated to all patients that have benefited, could benefit, or will benefit from the progress of this technology.

CONTENTS

PREFACE

Richard Zimmermann offers a very complete and didactic work to better understand nuclear medicine, an unknown medical discipline that touches on all fields of human pathology.

This book has the merit of addressing all aspects related to the diagnostic and therapeutic use of radioisotopes, by exhaustively describing the current clinical applications with an opening on the products under development. But it also explains in a pedagogic way what are the physical principles, technological developments, and regulatory constraints that apply to this field of medicine. This book is intended for the general public and will allow readers, be they neophytes, healthcare professionals, or health policy representatives, to better understand the huge clinical impact of this technique.

At a time when a certain radiophobia was developing in the world as a result of catastrophic nuclear accidents, it was important to explain the interest and the major contribution of nuclear power in medical practice. With this excellent work, Richard Zimmermann shares his knowledge and greatly contributes to the debate.

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INTRODUCTION AND DEFINITIONS

Nuclear medicine covers the area of a medical practice based on the resources of physics, its tools and products – nuclear meaning related to the nucleus of the atom – in order to be applied both for diagnosis and therapy. In both cases, a substance containing a radioactive isotope or **radionuclide** (one speaks about a radiolabelled substance) is directly administered to a patient. The radiolabelled product travels through the body to reach and accumulate specifically in a biological tissue or an organ. The concentration of this radionuclide in the targeted tissue or organ is favoured by the design of the organic or biological substrate, or **vector,** on which this radionuclide is grafted. Depending upon the type of emitted radioactivity, this product will be useful either to locate the targeted tissue or organ (diagnosis), or to initiate the destruction of these cells (therapy).

The term **radiotracer** refers to the notion of minute (trace) amounts of the substances in use, and also to the advantageous ability to "trace" the dissemination of the molecule in the body as a consequence of the linked radioactivity (light). The selection of the radionuclide is based on the nature of the emitted radiation, its physical properties, i.e. energy and half-life, and its chemical properties. They will define the final purpose of these molecules, called **radiopharmaceuticals**, among

which molecules dedicated to diagnosis are called **radiodiagnostics**. The diagnosis imaging technology – also called scintigraphy – is obtained by means of substances labelled with γ-emitter isotopes. The development of imaging acquisition technology associated with powerful information technology software has resulted in the development of the tomography technology, generating cross sections images and tri-dimensional pictures. Some radioactive elements can be used for therapeutic purposes thanks to their different physico-chemical properties; indeed, their short distance ionising effect leads to cell destruction. The use of these vectors in association with therapy radionuclides, essentially β-or α emitters, is called **vectorised** or **metabolic radiotherapy**. Such radiolabelled drugs used in therapy are also called **radiotherapeutics.**

The use of radioactivity generated by external sources (radiotherapy), including particle beam generators such as neutron therapy and proton therapy, remains under the control of radiotherapists. Hence, nuclear physicians have limited interactions with these technologies. The same applies to **brachytherapy,** also called **curietherapy**, a technology devoted to the use of permanent or temporary radioactive implants for the treatment of tumours. Still, these technologies will be described in this work. Finally, analogue sources (mainly X-rays) are used in **radiology** to obtain organ image data from different angles around the body; they are not part of nuclear medicine either.

1

Nuclear Medicine, What For?

After about seven decades of development and practice, nuclear medicine has recently reached a turning point. Indeed, over the past ten years, nuclear medicine has undergone three major technological breakthroughs directly impacting the way patients are handled. These three technical revolutions resulted from the implementation of very high capacity computer systems capable of handling the huge amount of data associated to the powerful imaging acquisition systems; the development of the system called hybrid imaging, and in particular the PET/CT equipment associated to the extension of the PET manufacturing network; and the demonstration of the efficacy and specificity of radiotherapeutics.

The new imaging modalities that appeared on the market at the dawn of the new millennium, as well as the new molecules and therapeutic technologies associated to radioactivity, open new and promising perspectives that fascinate experts from other medical disciplines – oncologists, haematologists and neurologists in particular. At the same time, the conventional pharmaceutical industry took an interest in these modalities – particularly in therapy; additional funding is now available for larger development programs.

This work does not intend to put forward new therapies and original answers to pathologies that seem hopeless. Physicians do have all the competencies required to prescribe the most appropriate treatments for specific patients and diseases. This book simply aims to provide detailed information with easily understandable words to a public most often unaware that such a discipline exists, and that it brings a new breath of life to diagnosis and therapy, especially in oncology.

For a long time, therapy by means of nuclear medicine was restricted to very difficult cases and last-chance treatments. Up to now, physicians recommended that metabolic radiotherapy should only be used after surgery, chemotherapy, and external radiotherapy protocols repeatedly failed. One forgets much too quickly that Iodine-131 has been used in thyroid cancer treatment since 1945. For the past sixty years, more than 90% of all thyroid cancers have been successfully treated – and most of them definitely cured – thanks to this nuclear medicine method. However, one ought to admit that, until recently, this therapeutic success was the only one reported in this field.

In most cases, nuclear medicine was essentially limited to being a support for diagnosis, mainly based on two different scintigraphy methods.

In this introductory chapter, we will see how patients can benefit from the knowledge acquired over the past half-century in the field of nuclear medicine, and learn about revolutionary new techniques and medicinal products. We will also take a look at all the opportunities offered by this technology in association to other innovative medical modalities.

WHAT DO WE CALL CANCER?

All living beings originate from a single cell which divides, grows, and continues to multiply while undergoing differentiation, in order to form the specific cells units of specific tissues and various organs that make up an individual. The production of these cells follows a complex predefined process, at a rhythm that is also predetermined. However, mature bodies stop expanding, and the production of new cells concentrates on specific growth mechanisms such as for hair or blood, and also as part of repair mechanisms such as skin regeneration or wound self-repair. The lifespan of a cell is limited; hence, its renewal is necessary.

Taking into account the impressive number of cells required to build a complete body, the process regularly deviates, giving birth to cells with unexpected structures. In addition, cells are continually subject to external stress and chemical aggressions – called the toxic effect – and this factor also interferes with the process of cell reproduction. Although the body is well-adapted to automatically correct or destroy these aberrant cells, sometimes such new entities find a more hospitable – or in any case less hostile – environment in which they can reproduce identically. When these new types of cells are not rejected by the organism, they create a new tissue called a tumour.

Tumours may either be benign or malignant. Benign tumours are not cancers, because they do not propagate themselves at the expense of neighbouring healthy and normal cells. If necessary, they can be easily removed without any consequence and without recurrence, and above all they do not represent a vital risk to the patient.

Malignant tumours, on the other hand, are composed of abnormal cells which divide and grow in a wild fashion, invading the tissue to the point of destroying it or preventing its proper functioning. Malignant tumours grow at the expense of neighbouring healthy cells, taking their nutriments. They divide, and grow to the detriment of healthy tissue, and at a later stage they spread and travel along the blood or lymphatic system, re-implanting themselves at remote places. This new distant cell colony, called

a metastasis, has the same properties as the original tumour cells, and will also continue to grow. In turn, these metastases invade and colonise other tissues, causing the disease to spread further again.
Each tumour cell is a malformation of a healthy cell of a very specific type. Therefore, it can be identified by the organ from which it originated. As the formation of a metastasis is only a remote colony, that is to say a relocated reproduction of these same cells, metastases of an identified type will display the same properties as the cells belonging to the original tumour. Thus, the primary tumour and the metastases of a tumour originating in the prostate will both be treated in an identical way, even if the latter are located in another organ far from the prostate. It is therefore important to determine the origin of a cancer – i.e. the primary tumour – in order to be able to treat the metastases, even long after the original primary tumour has been removed. A patient being treated for lung cancer and showing metastases of the liver is not suffering from liver cancer, but from a lung cancer that has spread. This person will be treated for lung cancer via a therapeutic protocol that greatly differs from liver cancer treatment.
Lymphomas and leukaemia are particular cancers that form in the blood precursor cells (hematopoietic system). These abnormal cells circulate in the blood and lymphatic systems, and reproduce to the detriment of blood cell production. They are sometimes called liquid cancers in order to be distinguished from solid tumour cancers.

I. THE ORIGINAL CASE OF THYROID CANCER

Iodine-131 has historically played a key role in nuclear medicine; we shall therefore start with this drug. The earliest imaging trials, followed by the first therapeutic treatments of hyperthyroid disease with injected radioactivity, began in 1942 under the control of American physician Saul Hertz. In 1946, he demonstrated that not only did thyroid tumours disappear following Iodine-131 treatment, but also all metastases, thus proving the therapeutic efficacy of this technique. This incontestable advantage is linked to the fact that thyroid tissue is the only tissue capable of absorbing iodine. This

fixation also includes the metastases, as these tissues are originating from the thyroid cells and are of the same biological structure as the originating primary thyroid cancer cells. Today, the injection of radioactive iodine remains essential for the diagnosis of thyroid diseases as well as for their treatment *(see Chapter 6, Section I below)*. Unfortunately, it remains the unique example of human tissue fixing a radionuclide in such a specific manner.

Nevertheless, iodine having demonstrated some additional physico-chemical advantages, isotopes from this family could be used for other applications in nuclear medicine when linked to active vectors.

II. THE DIAGNOSIS ASPECT

Nuclear medicine imaging is first of all a functional imaging tool used to check if a tissue or an organ functions, i.e. if it is alive. Contrarily to all other imaging modalities, only nuclear medicine can prove brain death for example. Magnetic Resonance Imaging (MRI), X-rays (X), or Ultrasounds (US) are unable to make the difference between dead and living tissues, and will only provide a nice three-dimensional image of the brain. Radioactive tracers will provide an image only from functional brain cells. Obviously, this imaging technology is not used in such an extreme case, and a cheaper electroencephalogram (EEG) will provide the same information in a simpler way. However, this example shows that this technology is extremely powerful as it can be used to monitor the functioning of the brain, the heart (necrosis, infarction), or the growth rate of a tumour invading a tissue *(Chapter 4)*. Therefore, almost every organ can be visualised in terms of biological function, and tracers are now available for nearly all tissues (bone, liver, kidney, heart, lung, gastro-oesophageal tract, etc.) and fluids (blood, cerebro-spinal fluid, urinary excretion tract, etc.). The nuclear medicine technology is a true functional imaging tool, whereas all other imaging technologies must be considered as morphological imaging tools.

The discovery of the utility of Thallium-201 in heart imaging, followed by the introduction of several Technetium-99m derivatives – both linked to the evolution of the image acquisition technology – made functional imaging an essential diagnosis tool in cardiology. Nowadays, cardiology care units very frequently use nuclear medicine; indeed, almost every person affected by an infarct undergoes scintigraphy. These tools give an accurate cardiac pump function check through a test called myocardial perfusion imaging.

Actually, the word scintigraphy stands for all of these two-dimensional imaging techniques *(Chapter 4, Section II)*. Cross-section images can be obtained by associating a rotating camera and a powerful computerised calculation system, called tomoscintigraphy. This technique – which brought a new dimension to the technology – has evolved in such a way that today three-dimensional imaging acquisition is possible. However, since the amount of data to be analysed increased simultaneously, medical applications had to wait until the end of the 90s – i.e. until the new calculator revolution – before they could take place in a realistic time frame with low-cost computers. Three-dimensional imaging was in fact limited by computer capacity, whereas the acquisition of signals was already well ahead.

The main pathologies that have benefited from these functional imaging methods include:

- imaging of the lung through a two-step process, with determination of the zones that can be reached by the inhaled air, and in parallel by the distribution of the blood arteries that will collect the oxygen in these alveolar areas (pulmonary embolism);
- bone scintigraphy, which allows to determine the metastatic zones and the development stage of a cancer at bone level;
- kidney scintigraphy, which allows to check if all renal filtration mechanisms are functioning properly (renal dysfunction);
- imaging of inflamed or infected tissues (in case of internal lesions, polyarthritis, appendicitis, etc.);

– and of course, localisation of all tumours and metastases which usually require a different molecule per type of tissue.

More recently and in addition to oncology, cardiology, and infectiology, functional imaging proved to be efficient in neurology, and tracers are now available to diagnose neurodegenerative diseases such as Alzheimer's and Parkinson's, in this case even before the clinical signs appear (*see Chapter 5, Section VI*).

A non-exhaustive list of available products is provided in *Chapter 4* with details on their use.

In parallel to computer development, a new technology called Positron Emission Tomography (PET) was introduced first in North America, and then in Europe. By the end of the 90s, the USA were the first to be properly equipped, whereas in Europe only Germany and Belgium had an adequate equipment network. The introduction of this new technology took longer in France, Spain and Italy – until 2001. At that time, some industries took the risk to install the specific and expensive manufacturing equipment while some governments arranged for dedicated cameras to be installed in public hospitals. The growth took a dramatic change in 2002 when the hybrid PET/CT system (PET cameras combined with an X-ray camera) was introduced. Today, in 2017, all developed countries are equipped, with over 5,500 PET cameras installed all over the world. Africa and South America, most Asian countries, and of course some remote places and islands are still behind in terms of equipment, but the progression continues. Actually, so far PET imaging technology could only be made available in a country where manufacturing sites for the powerful diagnostic drug fludeoxyglucose (or FDG) were also made available nearby *(Chapter 5)*. Some new technologies and generators (^{89}Rb, ^{68}Ga) may slightly change this constraint. In the meantime, this astonishing product has proven its efficacy as it offers unquestionable advantages:

– FDG is polyvalent. Its mechanism of action enables it to be integrated in any functioning or growing cell: in the brain and the

heart of course, but also in tumours and metastases, which grow faster than the other surrounding "healthy" cells;
- almost all cancer types can benefit from this technique and even some small metastases can be detected;
- FDG is easy to use. The radioactivity completely disappears in less than 24 hours thanks to the short half-life (less than 2 hours) of the associated radionuclide (Fluorine-18);
- patients are reassured by the fact the involved radioactivity has limited concentration levels, and this in turn enables physicians to use this tool when monitoring the efficacy of a given treatment;
- finally, it seems that the imaging quality is so good that even non-experts could read the images. As it turns out, this is not true since false-negative as well as false-positive results do exist also; still the image remains reassuring for both the physician and the patient.

PET technology together with its FDG tracer is recognised as being an extremely useful diagnosis modality for evaluating tumours, including head and neck tumours (particularly tongue cancers), pulmonary nodules, gastro-oesophageal cancers, differentiation between pancreas chronic inflammation and cancer, colorectal cancers, ovarian cancers, detection of bone marrow cancer metastases, melanomas, Hodgkin disease, and non-Hodgkin lymphoma. Disease extension (staging), chemotherapy or radiotherapy treatment response level, and actual possibilities of specific surgery can also be evaluated. Benign tumours can often be easily differentiated from malignant ones. This modality could be used to evaluate breast cancer, but other available techniques can provide equivalent information at a lower cost. In the latter case, FDG remains an interesting tool to estimate the extension of the disease, and even to monitor patients at risk of relapsing. However, this technique proves less interesting when diagnosing renal or prostate cancers since more efficient imaging technologies are available for these diseases. It has overall been proven that the decision of therapy differed from about 25% up to 70% in certain

cases when based on a FDG scan compared to a non PET-based diagnostic. Consequently, FDG is a powerful tool in selecting the best therapeutic protocol, reducing risks of complication, and limiting the treatment time frame.

It must be reminded that there is a difference between this non-exhaustive list of indications and the official list approved by the authorities as part of the FDG Marketing Authorisation *(Chapter 5, Section V)*. Important efforts have been made by clinicians to demonstrate that the not yet approved indications are valid on a larger population level, and that their integration in the official list could take place within the next few years. In reality, the use of PET technology differs from one continent to another, from one country to another, and even from one centre to another.

The latest technological revolution associates computer science with PET, thus resulting in the development of hybrid tools. PET/CT cameras which combine a three-dimensional PET detection system with X-ray tomography equipment can generate images in which the distribution of the FDG tracer can be superimposed with a three-dimensional view of the body. The localisation of the tumour becomes much more precise to such an extent that, for example, surgeons can better outline the tumour excision area; its removal is improved and healthy tissue can be preserved as a consequence.

First and foremost, the association of PET and FDG is dedicated to oncology. Nevertheless, FDG can be useful in analysing some brain functions (definition of the affected areas or brain damages following a brain stroke, evolution of neuro-degenerative diseases) or cardiac functions (viability of the cardiac tissue following a heart stroke). Nowadays, due to the limited access to this technology, it still is rarely used for these indications.

On the other hand, PET is a highly valuable tool for the study of brain function, and the development of new positron emitter labelled tracers other than FDG and specific to neurological mechanisms results

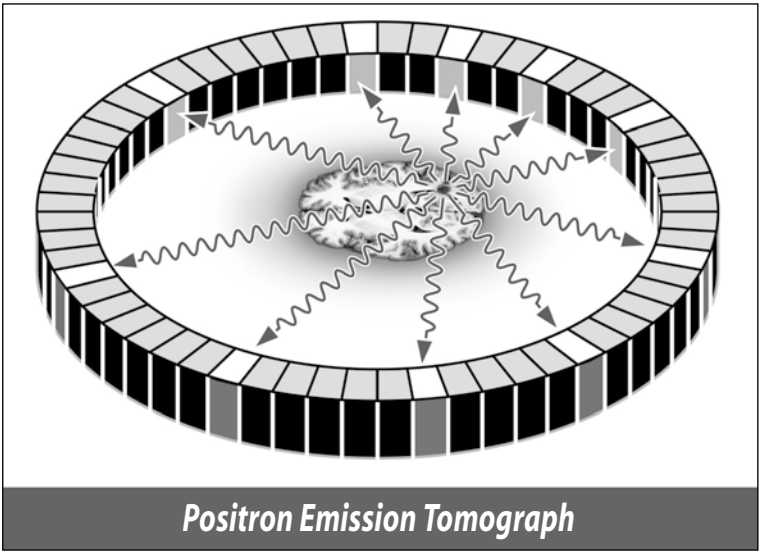

Figure 1 | The annihilation of positrons colliding with electrons results in the emission of gamma photons. Those rays are taken into account by detectors placed on a level plane; this enables the acquisition of a section image of the radioactivity source (the diagram shows the section of a brain with a tumour). The image of the whole body is reconstructed by superimposing hundreds of such cross sections.

in improved diagnosis accuracy for neuro-degenerative diseases such as Alzheimer's, Parkinson's, or Huntington's. The development, in parallel, of MRI technology becomes a necessity for patients affected by these diseases, and a very recent development led to the launch in 2012 of the hybrid PET/MR systems (PET technology combined with Magnetic Resonance Imaging), showing higher efficacy in neurology diagnosis than with PET/CT.

On the neurology side, a few new substances have already been marketed, but they are only used in very difficult cases. As of today, these diagnosis drugs are based on SPECT technology involving gamma emitters for imaging of Parkinson patients and epileptic patients, with PET technology for Alzheimer's patient imaging. In

fact, a whole new research field has emerged due to population ageing.

III. THE THERAPEUTIC ASPECT

Apart from some rheumatology affections, the therapy is mainly devoted to oncology in a large manner (including haematology). Therapeutic applications can only be destructive, not reparative. Cancer is ideal in the sense that the target is to destroy the abnormal cells – in this case the tumours. In certain places, metabolic radiotherapy has even been called a technique of 'nanosurgery'.

1. Cancer Therapy

Beta-minus, beta-plus, and alpha rays induce cellular destruction that can be used to our advantage in order to destroy unwanted cells. On the contrary, radioactivity cannot be of any help in pathologies for which cells have to be stabilised, and even less so when these cells have to be regenerated. Only abnormal or supernumerary (excrescence) cells (tumours) are targeted.

Tumours can in fact be destroyed under the effect of a powerful external beam of radioactivity (RX, α, β^-, γ, neutron or proton), but this technique is part of the external radiotherapy which is the domain of the radiotherapist, not of the nuclear physician.

Internal or metabolic radiotherapy, which is part of the therapeutic nuclear medicine, consists in injecting a patient with a radioactive substance that will be integrated in the cells to be destroyed by radiations *(Chapter 6)*. Iodine-131, described in the introduction as a useful thyroid cancer therapy, is probably the best example of this process. In recent years, new molecules have appeared that proved their real efficacy concerning some very specific pathologies – efficacy which can be observed in the treatment of patients affected by non-Hodgkin lymphoma and resistant to standard therapies *(Chapter 6, Section III)*. New prostate cancer treatment approaches involving

Radium-223 have also recently proven effective in terms of pain reduction and survival. The treatments for less common tumour pathologies (pheochromocytomas, neuroblastomas, polycythaemia, thrombocythaemia, etc.) and for chronic lymphocyte and myelocyte leukaemia had been known for a while, but the number of treated patients was directly linked to the very low incidence of these diseases. Some cases of non-transplantable liver cancers also benefited from a particular radiotherapy protocol in care centres well-known for their expertise in this domain. Finally, it was demonstrated a few years ago that in the absence of a total recovery, specific radiolabelled substances could significantly reduce the pain caused by bone metastases.

Today, these therapies are either restricted to patients in classical therapeutic failure mode, or to very limited and well identified patient subgroups. In the past five years, metabolic radiotherapy has greatly demonstrated its first-line efficiency on a larger scale, and new radiotherapeutics have recently reached – or are on their way to reaching – the market (prostate cancer, neuroendocrine tumour cancers). An excellent treatment for non-Hodgkin lymphoma has been available for more than ten years.

Other new molecules also undergoing clinical trials will be available in hospitals from 2017, particularly for the therapy of neuroendocrine tumours, prostate, lung, or colon cancers, lymphoma, myeloma and leukaemia.

Great progress has also been made in radioactive tracer assisted surgery techniques. Breast cancer has benefited from the most innovative and effective one, namely the sentinel lymph node detection (*Chapter 4, Section III),* which proved to be equally efficient with melanoma patients. Should this technique be implemented for all breast cancer patients, it would result in a dramatic decrease of cancer recurrence. Moreover, this technique is a lot less traumatic than surgical lymphatic system ablation – which is the current procedure.

TREATING CANCERS

Today, several increasingly effective cancer treatment methods are available to physicians. In the last ten years, oncology has reached a decisive turning point and undergone its own revolution. All issues have not been solved yet, but great steps have been made for the benefit of patients. There exists a typical, efficient, and well-defined therapy protocol for each cancer, once the development stage has been correctly evaluated.

For their own well-being, patients should know which therapy will be applied to them, and what it involves. More importantly, they should be warned of any potential side effect in order to anticipate, and wherever possible, alleviate them. Should the slightest doubt persist, patients are free to get a second opinion from another specialist. That specialist generally finds a sufficient base in the first analysis and evaluation to give his own opinion.

Therapeutic methods are quite numerous; this shows both the complexity of care and the lack of a universal treatment. Let's take a quick look at the current available treatments.

Surgery

The initial idea of physically removing a tumour is also the oldest method. A tumour mass can be removed extremely cleanly with surgery. In order to ensure that the tumour has been completely removed, as any tumour cell residue could re-colonise the area, surgeons must also take out some of the surrounding healthy tissue. If a tumour is well localised in uniform tissue, its removal (excision) can be carried out in an extremely clean manner. The surgical removal of tumours is common in breast, colon, liver, and even lung cancers; however, tumours prove more difficult to remove in the head and neck – and almost impossible in the brain. This is also the case with melanomas, or surface tumours, but unfortunately the operation leaves a large scar as it usually necessitates the removal of a relatively wide and deep area of skin. In spite of the unsightly scarring, this type of situation is ideal; however, it does not occur very frequently.

A growing tumour can spread to the surrounding tissue, making surgery more delicate. A melanoma on the foot, in direct contact with tendons or bone, is more difficult to treat than if it were on the thigh. A prostate tumour extending beyond the prostate and touching the bladder raises other problems. Therefore, the decision to operate depends on the size of the tumour, its location, the patient's general health condition, and the method of surgery required, including the type of anaesthetic. A surgeon can only remove what he can see, that is to say, the primary tumour, and any visible metastases if they are not numerous. When the disease has developed too far or has spread, another therapy has to be envisaged, or a complementary therapy must be integrated in the protocol.
Side effects are the same as with traditional surgery, and are linked to the consequences of the anaesthesia as well as to the fatigue generated by the healing process.

External Radiotherapy
A certain analogy can be drawn between the use of radiation to destroy a tumour and surgery in the sense that the beam of radiation replaces the scalpel. In the same way, intense cold or a laser can be used to burn tissue. Nevertheless, it is not a question of removing the tumour, but rather of destroying the malignant cells on-site.
In the external radiotherapy technique, a beam of high-energy beta or gamma radiation or X-rays is directed against the tumour mass. The treatment is applied to both surface tumours and internal tumours. As the beam is not selective, it destroys many cells as it passes over them – including healthy cells. In order to overcome this problem, a deep tumour is bombarded from various angles; therefore, the tumour itself receives a cumulative dose whereas healthy cells only receive a fraction of the radiation. The radioactive source revolves around the patient in a predefined path according to the size and shape of the tumour. The tools used nowadays have become so precise that the technique is applied when surgery becomes too invasive, or else for delicate procedures (e.g. brain

tumours). The treatment spans over several sessions that are spaced out in time. The procedure is not painful, but patients may feel tired. The irradiated skin may be affected (change of colour and irritation) and hair in this area may fall out. A combination of surgery and radiotherapy is often suggested. The cells are then subject to intense radiation designed to reduce the overall size of the tumour mass, which can then be removed more easily by the surgeon. Radiations can be applied after surgical removal, in order to complete the destructive process on very small tumour cells that could not be seen or were not accessible for the surgeon.

A new variable high-energy protontherapy technology (beam of protons) is now being implemented in some countries. This very expensive equipment has the major advantage of limiting the energy deposition in the tumour alone, with an accuracy to within one millimetre – thus preventing damage to many surrounding healthy cells. Its use is primarily intended for eye, brain, as well as children cancers, but its applications are extending as well.

Internal Radiotherapy

When the option of accessing certain cavities and introducing a source of radiation into them is available, this method – also called curietherapy – is preferred. Cervix cancer is one of the internal radiotherapy's target diseases. A radioactive implant is temporarily placed in contact with the tumour. Obviously, the radioactivity completely disappears as soon as the implant is removed. Brachytherapy – an extension of curietherapy – uses implants which are permanently placed in the tissue. Brachytherapy is mainly used in prostate cancer (radioactive seeds) or non-operable liver cancers (radioactive microspheres).

Chemotherapy

This well-known technique consists of using toxic substances to destroy the undesirable cells. Considerable progress has been made in this field, the main difficulty being to find molecules that destroy the tumour mass selectively without affecting healthy cells. Today, these drugs are

similar to any other drug in their form (pills, injections), and the term chemotherapy has become inappropriate; indeed, it could be applied to many drugs that treat by destroying, such as antibiotics, since it entails using a toxic chemical substance to destroy a cell.

One substance on its own does not do all the work. In order to ensure that a treatment protocol is effective, with a number of mechanisms acting at tumour cell level, it is preferable to give patients several active substances (a cocktail); these substances must be taken over a period of several months in a specific order, and in doses that are pre-established and of proven effectiveness (the protocol). It is important that this protocol is followed scrupulously, because it takes into account the evolution of the tumour mass over the course of the treatment. It is a race against the disease which involves a chemical substance that must destroy the cells faster than they can reproduce, while at the same time avoiding damage to surrounding healthy cells.

Most chemotherapy treatments are based on cell renewal mechanisms. The aim is to prevent the tumour mass from developing by blocking its reproductive and cell division system, while at the same time destroying existing cells. Tumour cells reproduce faster than normal cells; this is why they are able to spread more quickly and grow to the detriment of healthy cells. As the reproductive mechanisms of tumour cells are identical to those of healthy cells, some healthy cells that reproduce as quickly as the tumour cells are also affected. Thus, the otherwise regular growth of hair is blocked. The same goes for cells lining the stomach and intestines. These mechanisms explain hair loss and digestive disorders.

Therefore, a complementary treatment is prescribed along with the chemotherapy; in particular, substances are given to calm nausea and limit vomiting. Chemotherapy also affects the reproduction of blood cells (red and white corpuscles, platelets), which must be counter-balanced by transfusions. Once treatment is over, patients are given substances to accelerate the regeneration of these blood cells.

Chemotherapy is invariably exhausting and often depressing; therefore, an optimistic environment is more than necessary.

Hormone therapy is a special type of chemotherapy based on blocking the access of tumour cells to certain hormones they need for growth. The method either acts on the capture mechanism of these substances or on their production mechanism, sometimes going as far as eliminating the source of these hormones (ablation of the testicles or the ovaries).
In immunotherapy, the body's immune system activity is encouraged with elements designed to naturally fight the invasion of foreign cells. Interferon and the interleukins are products which have already shown advantages in cancer therapy.

Metabolic Radiotherapy and Radioimmunotherapy
Radioactivity can be considered as just another form of toxicity. If this toxic effect can specifically be directed against tumour cells, then radiotherapeutics are efficient. To reach this target, a radioisotope is attached to a molecule – or vector – capable of recognising cancerous cells. The vector helps in building a link to the tumour cell while the radiation simultaneously destroys it. The product is injected intravenously; it must be capable of concentrating in the tumour cells wherever these may be located in the body. This is the principle behind the usage of therapy radiopharmaceuticals, taking advantage of the metabolic mechanism of a cancerous cell or of the immune system, and becoming involved in its biological behaviour. The therapeutic part of this book takes a closer look at this principle. Generally speaking, as with a number of new products in the evaluation process, patients may be offered a treatment that has not yet totally proven its efficiency, but from which a certain degree of improvement is expected. Traditional protocol advantages are guaranteed to patients, who can expect health improvements at least equivalent to those expected had they not agreed to take part in this clinical study. All patients are free to accept or refuse participation in a clinical study; should they agree, they must sign a document indicating their "informed" agreement.

2. Non-oncological Therapeutic Application: Rheumatology

Therapeutic nuclear medicine is mostly devoted to cancer therapy. Even if the patient initially consults a specialist of the affected organ (a gastro-enterologist for a stomach cancer, a hepatologist for the liver, a urologist for the prostate), the therapeutic follow-up will eventually take place in hospital under the responsibility of an oncologist (or haematologist).

Among all the other slowly evolving diseases that could be taken into account by nuclear medicine, only rheumatology has found some practical applications with this technique. Rheumatoid polyarthritis remains the best example of this, as solutions were found independently of the type of affected joints simply by using different radionuclides with similar properties: this technology is called radiosynovectomy *(Chapter 6, Section II)*. Despite its efficacy, this treatment is not used to a large extent as only a limited number of centres are equipped to perform this modality.

IV. MISCELLANEOUS ASPECTS OF MEDICAL RADIOACTIVITY APPLICATIONS

In order to understand nuclear medicine as a diagnosis modality available for every human organ and tissue, and to appreciate its therapeutic benefits in probably every cancer pathology, it seemed that delving deeper into the principles of this not so well-known science and taking a closer look at its constraints, regulations, technologies, costs, limitations, and hopes would be beneficial to all of us. In order to facilitate reading, most of the technical and scientific words are explained in detail in a glossary at the end of this book.

The first chapter provides some basic knowledge on the different types of radiation used in nuclear medicine, and also on the risks linked to radioactivity (*Chapter 3*); then we take a look at the techniques and products used for diagnosis (*Chapters 4 and 5)* as well as for therapy (*Chapter 6)*. Taking into account the interesting evolution of Positron

Emission Tomography, a full chapter is dedicated to this technology (*Chapter 5)*. *Chapter 6* is entirely dedicated to the emergence of new therapeutics. Given the great hope placed on new drugs, it seemed interesting for us to describe the entire development process of a radiopharmaceutical, and more generally, of a drug (*Chapter 7)*. The application of these products, from the manufacturing tool to the injection to a patient, is detailed in *Chapter 8.* Finally, we will take a look into the future, far beyond the products currently under development (*Chapter 9)*.

Let us begin with a little historical background in order to recount the origins of the (very) young science that is nuclear medicine.

2

A Little History...

Nuclear medicine is not a vanguard technology in itself; indeed, its first applications appeared a mere few years following the discovery of radioactivity in the late nineteenth century. The development of this science benefited from the parallel evolution of three distinct technologies: nuclear physics beginning with the discovery of radioactivity right up until the development of radionuclides with well adapted half-lives and energy for clinical applications, radionuclide chemistry – i.e. chemistry allowing the incorporation of radioactive atoms into organic molecules, and eventually instrumentation with, in particular, the development of detection equipment as well as associated computers and software.

Nuclear medicine is an extension of the discovery of radioactivity that led to the development of the first radiology imaging technique. In 1895, Henri Becquerel (1852-1908; 1903 Physics Nobel Prize winner) made the chance discovery that certain substances such as uranium salts blackened photographic plates in the absence of light. At the same time, he observed that placing particular objects between this source (subsequently called radioactive) and this plate reduced the radiation intensity. In parallel that same year, Wilhelm Conrad

Roentgen (1845-1923; 1901 Physics Nobel Prize winner) developed equipment that could generate an unknown radiation – unknown because indefinable and original – which he called X. X-rays show similar properties to the radiation discovered by Henri Becquerel, but it would take a few years before scientists understood the true link between both of them. However, less than one year later, Wilhelm Roentgen succeeded in creating the first image of an X-rayed hand and demonstrated that human tissues behave differently depending on their density. This first radiography of Mrs Roentgen's hand, dating from 1896, became famous and opened the way for a new discipline of medicine: radiology. The recognition of the value and advantages of this technology was such that special radiology services were created within five years, and military medicine services in particular developed mobile imaging services.

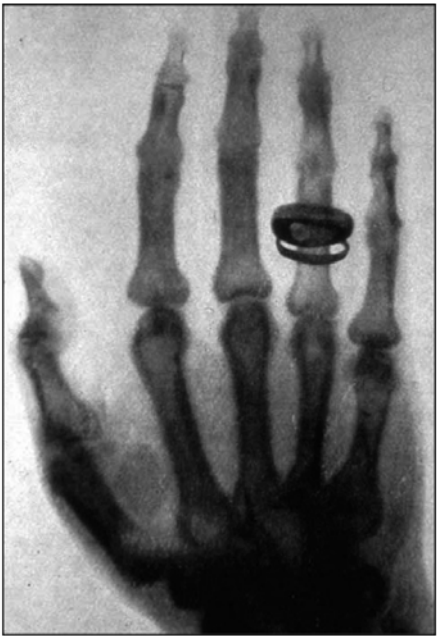

Figure 2 | Radiography of Mrs Roentgen's hand, taken in 1896.

The atom model, with its nucleus made of protons and neutrons around which electrons gravitate, was proposed by Ernest Rutherford (1871-1937; 1908 Chemistry Nobel Prize winner) in 1911. This model was improved in 1913 by Niels Bohr (1885-1962; 1922 Physics Nobel Prize winner). The concept of isotope was introduced in 1913 by Frederick Soddy (1877-1956; 1921 Chemistry Nobel Prize winner).

The first natural radioactive substances, radium and polonium, were isolated in 1898 by Pierre Curie (1859-1906; 1903 Physics Nobel Prize winner) and his wife Marie Sklodowska Curie (1867-1934; 1903 Physics Nobel Prize winner and 1911 Chemistry Nobel Prize winner). Following this discovery, numerous experiences were performed with uranium and radium. As early as 1900, German-born physicists Otto Walkhoff (1860-1934) and Friedrich Giesel (1852-1927) observed the effect of radium on the skin, which was similar to that seen a few years earlier with X-rays. Out of pure scientific curiosity, Pierre Curie repeated the experience by placing a radium source directly in contact with his skin during approximately 10 hours. The resulting red blotch transformed into a wound that would take 50 days to heal. Henri Becquerel accidentally observed the same result on his chest after having carried a sealed radium source in his jacket pocket during several hours. French physicians Henri Alexandre Danlos (1844-1912) and Eugene Bloch (1878-1944) made use of these substances as early as 1901 to treat cutaneous tuberculous affections. In 1903, American-born Graham Bell (1847-1922) suggested placing radioactive sources on tumours. This marked the beginning of Curietherapy, which would be developed later thanks to the works of Claudius Regaud (1870-1940) on radiosensitivity. This scientist laid down the basis of modern radiotherapy (use of selective radiation, multiplication of the irradiation focuses and areas, distribution of the radiation in space and time, calculation of optimal doses).

Precise radiation measurements were made possible with the discovery of special counters by Hans Wilhelm Geiger (1885-1945) in 1908-1910. The system was improved by Walter Muller in 1928

with the development of counting tubes which allowed quantification of these radiations. Later, these counters were replaced by scintillation crystals associated to photomultipliers (Samuel Crowe Curran (1912-1998) and William R. Baker in 1944, Hartmut Kallmann (1896-1978) in 1947, Robert Hofstadter (1915-1990; Physics Nobel Prize 1961) in 1948).

From then on, Georg Charles de Hevesy (1885-1966; 1943 Chemistry Nobel Prize winner) could follow the diffusion of radioactive substances, first in solutions, then in plants (1911). In 1913, Frederick Proescher published a first study on the distribution of radium injected intravenously with a therapeutic aim. In 1924, Georg de Hevesy, J. A. Christiansen and Svend Lomholt (1888-1949) used Lead-210 and Bismuth-210 on animals. On this basis, in 1926, Herman Blumgart (1895-1977), an American physician, injected himself a few millicuries of Bismuth-214 in order to follow his own blood circulation, and with the help of Saul Weiss he repeated the procedure with other volunteers and patients.

A vast area of research first saw the light of dawn in 1934, when the production of artificial radionuclides was discovered by Frederic Joliot (1900-1958) and his wife Irene Curie (1897-1956). The couple were awarded the Chemistry Nobel Prize in 1935 with this discovery, without which nuclear medicine would have quickly ground to a halt. Most of the natural radioisotopes – the only ones known at that time – were inadequate for medical applications due to their nuclear characteristics (radiation and half-life). As early as 1937, John Livingood (1903-1986), Fred Fairbrother, and Glenn Seaborg (1912-1999; 1951 Physics Nobel Prize winner) discovered Iron-59. One year later, John Livingood and Glenn Seaborg developed the production of Iodine-131 and Cobalt-60. Today, all three isotopes are still in use in nuclear medicine and radiotherapy.

Technetium-99, of which the metastable nuclide 99m is the most important artificial isotope in imaging, was discovered in 1937 by Emilio Segrè (1905-1989; 1959 Physics Nobel Prize winner for the

discovery of the antiproton), Carlo Perrier (1886-1948) and Glenn Seaborg.

In 1936, John Lawrence (1904-1991), brother of the cyclotron inventor Ernest Orlando Lawrence (1901-1958; 1939 Physics Nobel Prize winner), injected a patient with a radioactive substance, namely Phosphorus-32, for the first time as a treatment for leukaemia.

In 1938, Saul Hertz (1905-1950), Arthur Roberts and Robley Evans (1907-1995) performed the first research studies on the thyroid with Iodine-131. Then, for the first time and as early as 1942, they treated patients affected with hyperthyroidia. In 1946, on the same basis, Samuel Seidlin (1895-1955), Leonidas Marinelli (1906-1974) and Eleanor Oshry demonstrated that it was possible, following treatment with Iodine-131, to destroy all the metastases in a patient suffering from thyroid cancer. Later, Benedict Cassen (1902-1972) used radioactive iodine to demonstrate that thyroidal nodules accumulate iodine, thus allowing benign and malignant tumours to be differentiated from one another. These results had a major impact on the development of nuclear medicine as they demonstrated without the shadow of a doubt that this technique had great potential. Today, it remains the most efficient method in the treatment of thyroid cancer. In 1951, Iodine-131 in the form of sodium iodide became the first radiopharmaceutical to be approved by the Food and Drug Administration (FDA).

It was not until 1959 that radioimmunoanalysis methods, used to quantify tiny amounts of substances present in serums, were developed by Rosalyn Sussman Yalow (1921-2011, 1977 Physiology and Medicine Nobel Prize winner) and Solomon Berson (1919-1972). This technology provided the basis for *in vitro* biological analysis based on radionuclides.

As for imaging methods, one had to wait until 1950, when the linear scanner was invented by Benedict Cassen (1902-1972), to see a significant evolution. From that moment on, a sum of radioactive values measured around a body area could be transformed into

an image using this tool. In 1953, Gordon Brownell and William Sweet built the first detector to allow the coincidence counting of radiation emitted by positron annihilation. Hal Anger (1920-2005) developed in 1957 the gamma camera (scintillation camera), capable of measuring the radioactivity of a surface in one go rather than point by point as with the linear scanner. This technology has since considerably improved in terms of detector sensitivity and resolution, as well as measurement speed. As a result, the most recent equipment is able to provide computerised superimposable three-dimensional colour images. Tomography, the two dimensional imaging technique also called tomodensimetry, appeared in 1962 thanks to David Kuhl (1929-). The evolution of this technique resulted in the invention of Tomoscintigraphy, or Single Photon Emission Computed Tomography, and Positron Emission Tomography. At the same time, this technology was integrated to X-ray scanning tools: the result was the creation of X-ray Tomodensimetry or X-scan Computed Tomography. Hal Anger contributed to the development of other medical imaging tools, inventing the tomographic scanner, the full body scanner, and the positron camera. In fact, John Keyes initiated the development of the first SPET camera (1976) and Ronald Jaszczak (1942-) developed the first dedicated SPET camera. Positron emitters applications in medical imaging are mostly based on research conducted by Michel Ter-Pogossian (1925-1996) and Michael Phelps (1939-).

Technetium-99m found its first real medicinal application when the first commercial generators were made available by Louis Stang Jr. and Powell (Jim) Richards (1917-2010) from the Brookhaven National Laboratory in 1960. The first positron generator (Rubidium 82) was approved by the Food and Drug Administration (FDA) in 1989.

In 1963, Henri Wagner (1927-2012) obtained the very first lung images using radiolabelled albumin aggregates, and in 1973 William Strauss (1941-) introduced stress testing for cardiac imaging. A few

years later, in 1978, David Goldenberg (1939-) developed the first radiolabelled antibodies for tumour imaging – but the FDA did not approve this new product as being a medicinal drug until 1992.

Finally, the PET technology would never have reached its current stage of development without the improvement of the cyclotron technology, and overall without the discovery of the FDG (fludeoxyglucose). This molecule was synthesised for the first time by the team led by Al Wolf (1923-1998) together with Joanna Fowler (1942-) from the Brookhaven National Laboratory in 1976, on the basis of an idea by Lou Sokoloff (1921-2015) and Mark Reivich – who had already worked with Carbon-14-labelled glucose. The first image of a patient injected with FDG was obtained by the team involving Michael Phelps, Henry Huang, Edward Hoffman, and David Kuhl at the University of Pennsylvania.

The term "Nuclear medicine" itself was coined in the 50s by physician Marshall Brucer (1913-1994), who was actively engaged, along with the US Army, in favour of using radionuclides in medicine. As a teacher, he created a study programme in the US allowing physicians to get a degree as well as the very first authorisations to handle radionuclides within the medical field.

3

Some Basic Notions of Radiation

Natural radioactivity first appeared concomitantly to the creation of the earth, and the radionuclides that can still be found in soil today are in fact long period isotopes or decay nuclides dating from the original matter. As a consequence, man has always been exposed to environmental radioactivity, whether from terrestrial or cosmic origin, and of course we continue to find these radionuclides in our food and indirectly in each of our body cells. It then becomes essential to provide more details on the nature, origin, amount, and effects of this type of 'natural' radiation, as radioactivity has always been associated with risk and danger.

In particular, when discussing radioactivity hazards one must take into consideration the levels of both natural and artificial radioactivity to which man is exposed daily. Therefore, before taking a closer look at the effects of radiation on cells, let us start by explaining some of the words that are recurrent throughout this book, as well as defining the measurement units.

A radioisotope is an unstable atom that spontaneously transforms into another stable or unstable entity after a precise period of time, while simultaneously emitting energy in the form of particles or

radiation. The origin of this energy emission is called **radioactive source.** Radioactivity is subject to the **decay** phenomenon, in other words the reduction over time of the amount of emitted radiation. The **period** (or **half-life**) determines the length of time required before half of the existing amount of material turns into another isotope. The period is a constant for a given radioisotope, and can cover durations from a fraction of a second to several billion years. As a result of decay being an inverted exponential function of time, the activity of a source reduces to one tenth after only slightly more than three periods, and to one thousandth of its initial activity ($2^{10} = 1{,}024$) after only ten periods.

The word **radioisotope** should only be used for elements with the same chemical entity (Iodine-123, Iodine-124, Iodine-131, etc.), while the plural word **radionuclides** refers to every radioactive element from the periodical table. To simplify matters, the word "hot" may be used to describe a radioactive substance or isotope, as opposed to "cold" for a stable isotope.

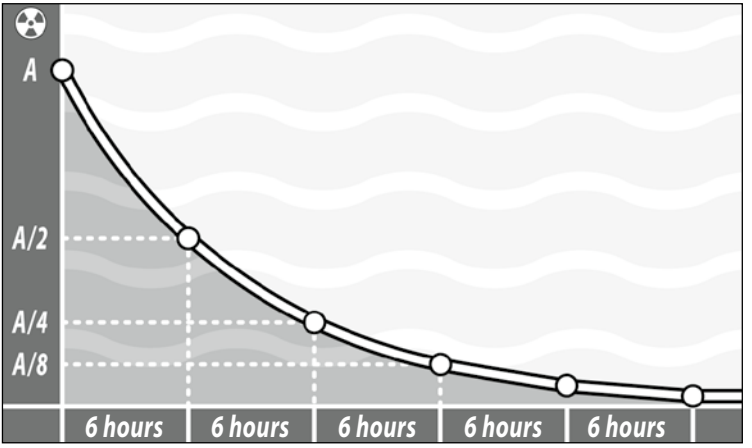

Figure 3 | Decay and half-life: a radioactive substance loses half of its activity (A) during each period (or half-life) following a very regular decay curve. The decay of Technetium-99m with its 6-hour half-life is given as an example. After 18 hours of decay, only one eighth of the initial amount remains radioactive. After 30 hours, there is only about 3% left (1/32).

Besides its half-life, a radionuclide is defined by two other parameters: its type of emitted radiation, and the level of energy associated with this radiation. These three characteristics, namely type of radiation, energy, and half-life, single out the radionuclides that are relevant to nuclear medicine among the thousands of known ones. The associated chemical and biological properties are decisive criteria of selection, independent of radioactivity.

I. DIFFERENT TYPES OF RADIATION

Four different types of radiation in particular have found an application in nuclear medicine, but other different types of radiation with greater therapy potential are beginning to emerge.

The **gamma** (γ) **ray** corresponds to the emission of short wavelength and variable energy photons. This radiation translates the loss of excessive energy in the nucleus and its transformation into a more stable state, as opposed to the production of X-rays obtained after excitation and ionisation of electrons. Gamma rays are ideal diagnosis tools. As they are very penetrating, they can go through large thicknesses of matter and travel hundreds of meters in the air. Dense materials such as lead, wolfram, uranium, very thick concrete, and deep water are able to stop them – or at least strongly attenuate them. The emitted radiation differs with each isotope, which makes for a more accurate identification of the originating radionuclide.

Beta-plus (β^+) **rays** correspond to positively loaded electrons called positrons. Positrons result from the transformation of a supernumerary proton into a neutron, neutrino, and positron, the latter being an anti-electron (or a positively charged electron). The weightless neutrino does not play a role in nuclear medicine. The mass of the resulting isotope remains unchanged, but its atomic number is reduced by one unit. The positive electrons emitted by the radioisotopes in the continuous energy spectrum will eventually collide with a negative electron along their ejection path. The collision

will lead to the annihilation of the matter and to a transformation into pure energy, in the form of two 511 keV photons (gamma rays) that have the particularity of travelling in two exactly opposite directions. If two detectors are placed on each side of the emission source, it becomes possible to calculate the precise origin of that source after several collisions. This method would be very precise if it wasn't for the fact that the resulting image represents the distribution of the collision sites, and not the positron emission sites. Some high-energy positrons can travel for several millimetres before encountering an electron, and then only producing their two photons. The analysis of the journey of all these photons forms the basis of the imaging technology, called **Positron Emission Tomography** (PET).

Beta-minus rays (β^-) are made of electrons –namely particles of identical mass to that of the positron –which are negatively loaded and travel at high speed. This radiation results from the transformation of an excessive neutron into a proton, electron, and antineutrino. The weightless antineutrino, like the neutrino, does not play a role in nuclear medicine. The proton participates to the reorganisation of the nucleus and to the transformation of the initial radionuclide into a new element with an atomic number increased by one unit. Only electrons are ejected in a continuous energy spectrum which depends directly on the radioisotope. These electrons can go through walls of several centimetres in thickness and travel several metres up in the air, but most of the time they are quickly absorbed by matter, where they can sometimes generate X-rays while their excess energy is transformed into heat. They also generate free radicals that can lead to molecular rearrangements; thus, they present a high destruction potential, and some radioisotopes selected for their specific half-life and energy can be used for localized cell destruction. Therefore, beta-minus emitters are efficient when used in therapy, mainly in oncology.

The ionising property of an isotope used in therapy is evaluated in the average penetrating distance that is directly linked to its energy. These values are comprised between a few millimetres and a few

centimetres, thus providing a choice among several radionuclides in order to find the most appropriate one to treat or destroy a tumour.

It is obvious that the higher the energy, the longer the penetrating distance, and consequently the higher the risk for healthy cells to be affected as well. At the same time, environmental irradiation risk levels increase.

A nucleus that decays when emitting beta rays can leave the resulting radioisotope in an excited state, which in turn will immediately emit gamma rays to return to its stable stage. In some cases, this excited state is itself stable for a well-defined and measurable period. Known as the **metastable** state, it is identified with the letter "m" next to the isotope's mass number. The best-known example of this is Technetium-99m, with a half-life of 6.01 hours. Technetium-99m is a pure γ emitter obtained after decay (and β^- emission) of Molybdenum-99 (half-life 8.04 days).

The **alpha ray** (α) corresponds to the spontaneous generation of a heavy particle consisting in a naked nucleus formed by two neutrons and two protons, which is in fact the nucleus of helium. This entity being 7,000 times heavier than the electron (*i.e.* β^- radiation), it is stopped by a very small amount of matter. Only a few centimetres of air absorb the radiation, and a simple sheet of paper is enough protection against alpha rays.

The alpha particle is stopped by organic tissue. However, it has a very high ionization potential compared to beta emission, and it is much more powerful in terms of cell destruction. It ionises the molecule and indirectly cuts it or allows it to be transformed chemically. If the molecule in question is a vital part of the reproduction mechanism (DNA or RNA for example), this interaction will usually result in the death of the cell.

X-rays (RX), correspond to the emission of photons (light) of a particular type as a consequence of the excitation of electrons. It was the first radiation to be observed and artificially produced, and it is mostly known as an external body imaging source. It gave birth to

radiology, which developed considerably further due to improved detector equipment and, later, to computer technology. X-rays can also result as a secondary radiation from the interaction between a high-energy beta minus ray and the matter in which it is absorbed. This secondary radiation – also called *Bremsstrahlung* – originates from the impact area between the electron and the matter, i.e. in the mass. If this reaction takes place in the protective elements, it can happen that the residual thickness left after the generation of the X-ray is not sufficient anymore, thus generating supplementary radiation protection issues.

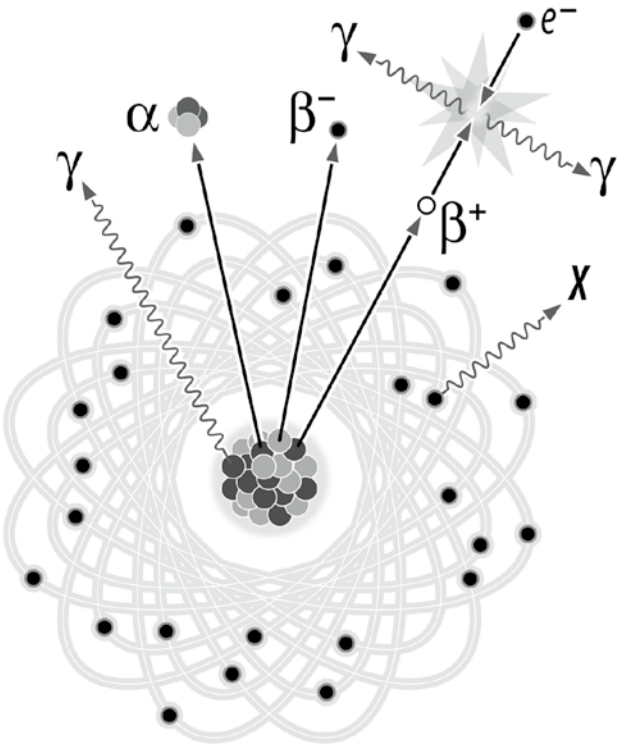

Figure 4 | The different radioactive radiation types used in nuclear medicine (gamma, beta-plus, beta-minus, alpha, and X-ray).

X-rays or γ rays can be generated as a consequence of the **electron capture** phenomenon. If the nucleus does not have sufficient energy to emit a positron, the proton in excess can be transformed into a neutron by trapping an electron gravitating too closely to the nucleus. The resulting empty space will itself be completed by taking another electron from a higher layer (orbital) and by emitting in parallel either X-rays or γ rays.

If the excess energy of a radio-transformation or **internal conversion** is transferred to another layer of electrons rather than via γ ray emissions, it can happen that an electron is ejected. These electrons – called **Auger electrons** – are much less energetic than β^-. However, they show a therapeutic application potential analogous to that of alpha emitters, as their sphere of activity is limited to a few tenths of a millimetre and they are consequently only useful for the destruction of a few cell layers.

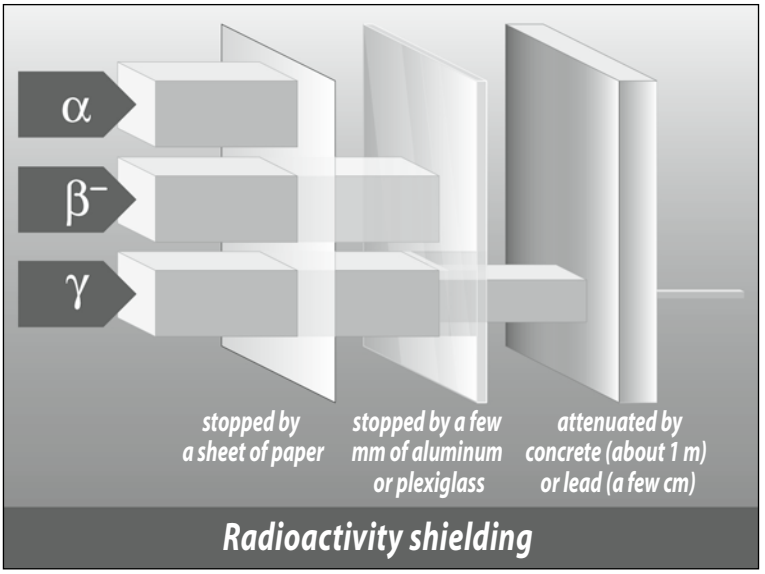

Figure 5 | Radioactivity shielding: the different radiations are stopped in different ways, depending on the shielding material and its density.

Neutrons (**n**) and **protons** (**p**) are also used within the framework of external radiotherapy techniques. These particles are generated with specific tools and their use represents a large part of the external radiotherapy technology, out of the scope of nuclear medicine.

Finally let us not forget that we, as human beings, are under the influence of cosmic rays from outer space (in particular muons, but also γ, n and X-rays) on a daily basis, and that, should the necessity arise, these rays could only be stopped by several tens of centimetres of lead.

In fact, only very few radioisotopes are emitters of a single type of radiation. Technetium-99m is an almost pure γ emitter, Fluorine-18 is a pure β^+ emitter, and Yttrium-90 is a pure β^- emitter. Most of the other radionuclides are emitters of at least two radiation types, most frequently β^- and γ or X-rays. If the γ part is not too high, the radionuclide will be found helpful for both diagnosis and therapy. If the β^- part associated to X-ray is sufficiently low, this isotope could be taken into consideration for imaging. The other physico-chemical properties of this element will then determine its usefulness in nuclear medicine applications.

Among the thousands of known radionuclides, more than a hundred are potentially interesting for nuclear medicine. Taking in account the cost of manufacturing and supply, the half-life of the radioisotope and the specific chemistry involved, only a few tens of radionuclides remain realistically usable. Let us therefore concentrate on these few radionuclides and demonstrate their real interest through examples.

II. MEASUREMENT UNITS AND DOSES

The activity of a defined amount of radioactive nuclide is measured in **becquerels** (Bq). One becquerel corresponds to the disintegration of one atom per second (the becquerel is a measurement unit that replaced the **curie** (Ci), 1 curie being equivalent to 37 billion

becquerels). Taking into account the fact that the radioactivity level emitted by these substances is usually high, unit multiples are more frequently used – megabecquerels (MBq, 10^6 Bq), gigabecquerels (GBq, 10^9 Bq), and terabecquerels (TBq, 10^{12} Bq) in particular. Doses injected to a patient for an imaging procedure usually range from a few hundred to a few thousand MBq. Depending upon the country and the habits, curies and millicuries continue to be used instead of GBq and MBq.

The emitted radiation transfers a certain quantity of its energy to the material or the tissue by absorption. This amount of energy is expressed in **grays** (Gy). Grays measure the **absorbed dose** and replace the former **rad** units (1 Gy = 100 rads). It is possible to link the emitted radiation to the absorbed one, but the equation must take into account the energy of the source, the distance to the source, the irradiation duration, and the nature of the radiation. This calculation is much simplified in the case of a fully absorbed source (e.g. when a dose is injected), as almost all of the radiation will affect surrounding tissues as long as the radiation has not decayed, or if the radioisotope is not biologically eliminated.

As it is mandatory to take into account the nature of the radiation and its effects on tissue, the absorbed dose will be corrected by a weighting factor in order to obtain an **equivalent dose** expressed in **sieverts** (Sv). Sieverts replace the former **rem** units (1 Sv = 100 rems).

ABSORBED DOSE, EQUIVALENT DOSE, AND EFFECTIVE DOSE

The effect of radiation on a given organism depends on the dose absorbed into the tissues, but also on the type of radiation and on the sensitivity of the irradiated tissues or organs.
The dose absorbed into the tissue or organ (**absorbed dose**), expressed in grays (Gy) corresponds to the quantity of energy imparted per unit mass of matter. One gray corresponds to one joule per kilogram.

The effect on the tissue will be different, however, depending on whether the particle is energetic or not. Photons generate other effects in the tissues than neutrons or alpha radiation. The absorbed dose is therefore corrected by a weighting factor which allows for the **equivalent dose** to be obtained. Thus X, γ, or β radiation are similar in their effects and do not need to be corrected (weighting factor equal to 1), while neutrons are assigned a weighting factor between 5 and 20 depending on their level of energy. The highest coefficient is applied to neutrons as their energy is between 100 and 2,000 keV, and reduces again after that. This is explained by the fact that very high energy neutrons pass through tissue so rapidly that they do less damage than if they passed at a lower energy level. Extremely ionising a radiation is in turn assigned a weighting factor of 20.

Tissue sensitivity must also be taken into consideration, because each organ reacts differently to radiation. From this is deduced the **effective dose** which is quite simply the sum of the equivalent doses corrected by a weighting factor according to the irradiated tissue. The most sensitive tissues are quite obviously the gonads (weighting factor of 0.2), followed by bone marrow, the colon, the lungs, and the stomach (0.12). A factor of 0.05 is assigned to the bladder, the breasts, the liver, the oesophagus, and the thyroid, and 0.01 to the skin and the bone surface. At an equivalent dose, the effect on the testicles would be twelve times greater than on the skin.

These coefficients enable the calculation of external and internal exposure dose limit values for people working with nuclear substances. Effective dose limits are currently set at 20 mSv in Europe, but new texts currently in progress will further lower these values, probably around 12 mSv. The accepted limit for the population is set at 5 mSv.

A man ingests on average 100 Bq of Carbon-14 per day (half-life 5,730 years) and almost as much Potassium-40 (half-life 1.3 billion years). The latter accumulates in bones and alone accounts for about 6,000 Bq in a 75 kg adult. On the other hand, due to the constant

equilibrium preservation of the different salts present in body cells (homeostasis phenomenon), potassium does not accumulate in the human adult body anymore, and its content remains therefore stable. Excess is eliminated through urine. As a consequence, the average radioactivity of an adult human body stays around 150 Bq/kg, which brings the radioactivity of an adult at around 8,000 to 10,000 Bq. In other words, about 8,000 atoms degrade every second in each individual .

In order to provide information on the effect of natural radioactivity on man, it is easier to compare equivalent doses using sievert units. External radiation as received by man, of terrestrial origin and caused by non-ingested elements such as soil radioactivity, accounts for about 0.4 millisieverts (mSv) over one year. The ingested part, which irradiates the body at one hundred percent, participates to 0.3 mSv – among which 0.18 are solely due to the Potassium-40 mentioned earlier. A man also inhales radioactive gases, in particular radon and its daughter radionuclides, as they emanate from naturally radioactive material such as granite present in concrete, in the walls of our homes, etc. These gases are a cause of supplementary internal irradiation and represent between 1 and 20 mSv over a year in total, depending on location. A figure of 1.3 mSv is usually taken as an average value.

Cosmic radiation contributes to 0.4 mSv for our yearly irradiation on average, but this value highly depends on altitude. It can vary from 0.3 mSv at sea level up to 2.0 mSv at 5,000 metres in altitude. Doses absorbed by passengers during a flight, and at extreme levels by astronauts, are even higher.

The sum of all these individual values reaches approximately 2.4 mSv, which corresponds to the average radioactivity dose as absorbed by a European or American individual living in an area with a sedimentary soil containing only little amounts of radioactive substance. In the following paragraphs, we will use this value as reference when comparing the different doses from artificial (medical) origins to which patients are subjected. It is obvious that this figure must be adapted depending on whether one lives by the seashore or

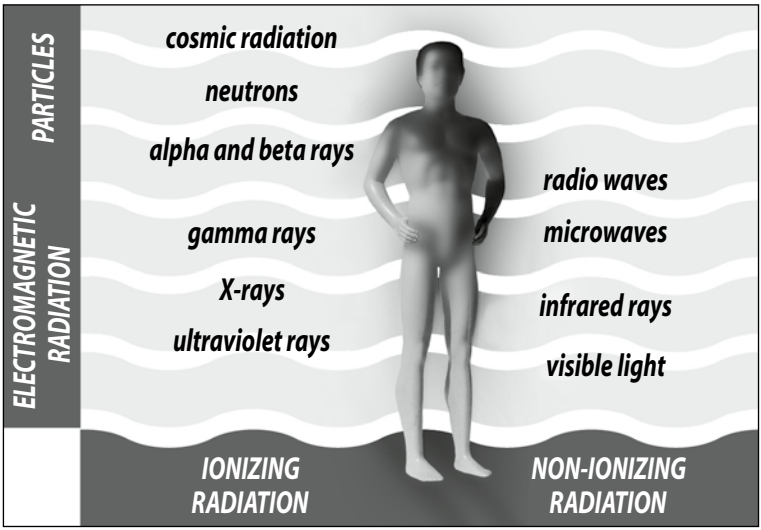

Figure 6 | Different types of radiation to which man is daily exposed.

in the mountains, on sedimentary or granitic soil, near a coal or a uranium mine, in the Equator or the North Pole.

In particular, as this value is an average figure, one can already try to compare it with some extreme natural radioactivity values, as found in certain regions and to which local inhabitants are subjected daily. In some areas soil radioactivity can be close to zero, while in others it can reach 1.5 mSv. In granitic areas, as well as in the mountains, the annual average is around 3.0 to 3.5 mSv. In Brazil or in Iran, inhabitants of zones with naturally high concentrations of uranium or thorium can accumulate up to 100 mSv per year. Similarly, high concentrations of radon in closed areas such as poorly ventilated cellars can make doses soar up to 500 mSv per year. In terms of cosmic origin radiation, more precise measures have been taken for people living in altitude. Mexico's 20 million inhabitants, located at 2,240 metres in altitude, annually absorb 0.82 mSv, while this figure reaches 1.7 mSv for the 400,000 people living in Lhassa,

Tibet (3,600 metres), and 2.0 mSv for the million Bolivians in La Paz (3,900 metres).

Let us remind ourselves at this stage that natural and artificial radionuclides differ in that the former has been in existence since the creation of the Earth, i.e. from "natural" origin, whereas the latter was first produced by man with appropriate tools in the late 30s. On the other hand, there is no difference between radiations of natural and artificial origins as they both have the same effect on inert or living matter, with results which do not allow any origin identification.

The discovery of new radioactive (artificial) isotopes is described in details in the history chapter. Radioactivity is a source of energy that – like all other energy sources (water, fire, charcoal, electricity, etc.) – can be used by man for practical purposes or on the contrary, for its destruction power. Thus, the development of nuclear physics has led to the creation of new weapons, and in parallel to the discovery of new and efficient treatments for patients affected by specific incurable diseases.

Today we must take into account the fact that artificial radioactivity does exist, and therefore must be integrated in the calculation of the doses accumulated by man on a yearly basis. Thus, aerial nuclear weapon assays that were performed in the past now account for a yearly average of 0.10 mSv. The total of today's nuclear industrial activity, production of electricity included, adds another 0.02 mSv on average. Nuclear medicine and medical imaging in general, including chest radiography, contribute for each individual to a dose of approx. 1.00 mSv. As a consequence, one has to add 1.10 mSv of artificial radioactivity on average to the above-calculated dose of natural radioactivity. As for natural radioactivity, this figure must be modulated depending on whether one lives near a nuclear power plant or works in a radiology imaging unit.

In fact, when people aren't normally in direct contact with radioactivity as produced by the nuclear industry, the highest dose absorbed usually originates from medical examinations. A chest X-ray

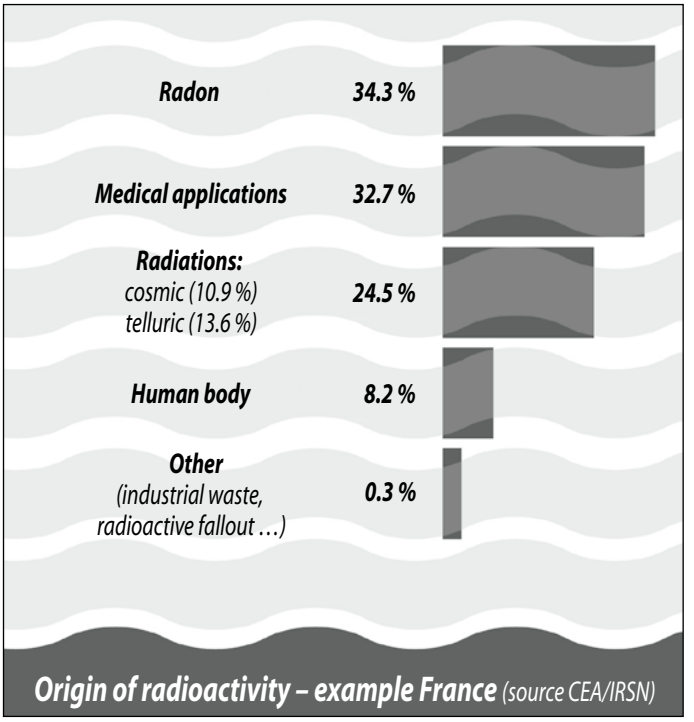

Figure 7 | Distribution of radioactivity to which man is permanently exposed.

imaging gives an equivalent dose of 0.2 to 0.4 mSv to the patient. Technology improvements over the past fifty years have reduced this dose by a factor of 20, and it continues to drop. In comparison, the dose inflicted by an abdominal scanner is about ten times higher, while a dental radiography corresponds to approx. 0.002 mSv efficient dose per image.

As nuclear medicine is a technique which implies the injection of a radioactive substance, one may expect greater figures. However, those figures remain low because very small radioactive tracer amounts are sufficient to generate the required image. Evaluating the irradiation levels is a difficult task, as it depends on the distribution of the

tracer throughout the different tissues and organs. The equivalent dose is estimated at a few millisieverts and remains below a dozen of millisieverts for a myocardial perfusion scintigraphy. In these cases as well, imaging technology improvements – concerning detectors sensitivity in particular – have since the 50s enabled a drug dosage as administered to a patient for a given examination to be divided by a factor of ten to one hundred.

On the other hand, the amount of doses that can be used in therapy is limitless as it aims to destroy cancerous cells. Well-controlled methods of radiotherapy allow for the equivalent of tens of sieverts to be administered, thus confirming that high doses of radioactivity can save patient lives.

THE RISKS OF RADIOACTIVITY

As with any source of energy, radioactivity presents risks that are obviously a function of the dose absorbed by an individual. Injecting a radioactive substance into a patient is not a trivial procedure. It is possible because decades of experience in this field have helped define the limit separating the beneficial effects from the harmful effects, even if this frontier still remains extremely imprecise.

The effects being a function of the dose, distinguishing acute irradiation (accidental, radiotherapy, etc.) from chronic exposure (natural radioactivity, radioactive ambient environment, nuclear industry, etc.) is paramount.

At this stage it is essential to remember that there is no difference between radioactivity of natural origin and radioactivity of artificial origin. The resulting radiation and consequent effects are one and the same. The difference lies in the quantity, the period of exposure, the energy, and therefore the actual dose absorbed. By analogy, everyone agrees to say that UV radiation emanating from sunlight has the same beneficial or damaging effects as that emanating from artificial light.

At low doses, some researchers hypothesise that radioactivity would even be of benefit to a healthy person, but for the moment the scientific community has not yet succeeded in reaching an agreement on the subject. The theory would have it that very weak levels of radioactivity contributed to the evolution process of animal species, and therefore man, and still participate today in cell selection mechanisms and in the creation of self-defence systems via immune system stimulation. This theory is called "hormesis", and seeks to demonstrate that very small amounts of radioactivity are actually beneficial for the health. It must be acknowledged that scientific proof is very scarce due to the difficulty of measuring these weak doses and their impact. Only statistical studies covering a very large population can give any hints.

What is certain is that radioactivity causes mutations that lead to the formation of cancerous cells. The minimum dose – the threshold – required to generate a micro-tumour remains unknown. It is clear that the initial radiation is not responsible for this evolution, since we are bathed in radioactivity on a daily basis. It should be noted that the average level of ambient radioactivity on our planet has decreased by a half since man appeared.

A parallel can again be made with this other form of radiation: sunlight; man clearly needs the sun in order to survive (for example for vitamin synthesis via the skin), but over time, it has been proven that this same sun also causes the appearance of melanomas. It is completely impossible to evaluate the minimum period of sun exposure required to generate a melanoma, and from there, the period of time that should not be exceeded to avoid with certainty any risk of developing this form of cancer. The answer depends on each individual and cannot be determined in advance.

Similarly, the radioactivity effects vary with each individual, and the actual observed effects are based on the minimum values (and not the average values) from which a disturbance has been noted. It is considered that, for an adult, less than 100 mSv over the whole body constitutes a weak dose. For an even exposure over the body, initial clinical effects have been noted from 250 mSv in the form of nausea

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and a slight drop in the number of red blood cells. Blood count changes above 1,000 mSv, and one person in two will die if the dose exceeds 2,500 mSv. When the irradiation is local the effects depend on the organ or tissue affected, and the cells in direct contact will be the most affected (skin and eyes in the case of irradiation, skin in the case of contamination, lungs in the case of inhalation).

These values serve as a reference for physicians when treating patients. In the case of imaging, doses remain well below the theoretical risk values. In the case of therapy, the rules are different since the aim is to destroy the supernumerary or cancerous cells. Very strong doses may be applied as they alone can lead to healing. The selectivity of the vector, the reduced retention time in healthy cells, and the speed of elimination all contribute to the maximum reduction of the risk of causing a new cancer.

For staff working in a radioactive environment, the ALARA rule (As Low As Reasonably Achievable) takes precedence and is applied in all sectors of the nuclear industry, in the radiopharmaceutical industry, and in the nuclear medicine departments of hospitals. For, in the end, the most exposed people are not those who are injected with a radioactive substance once or twice in their lives; actually, the people most at risk are in daily contact with either these substances or with patients undergoing radioactive treatment.

III. RADIONUCLIDES FOR NUCLEAR MEDICINE

Radioactive isotopes of interest for nuclear medicine (more aptly called radionuclides as isotopes refer only to one type of atoms – e.g. the iodine isotopes – whereas nuclides take every periodic table element into account) are characterised by their half-life, their type of radiation, their energy, and their chemistry. The half-life must take into account the imaging technology and conditions (acquisition time) and the biological elimination process (effective presence in the human body), as well as production, logistics, and waste management constraints. When a half-life is shorter than two hours, it is not seriously conceivable to run a production and a distribution phase of the drug

without huge product losses – therefore impacting the cost. Half-lives which are higher than one week raise new problems in terms of storage and waste storage or treatment. The radiolabelled drug or tracer will be injected, swallowed, or inhaled, and the elimination rate from the body must be sufficiently fast to avoid any negative consequences on healthy human tissue. Finally, the radionuclide energy must be adapted to the needs of both the patient and the physician.

1. Gamma Emitters (γ)

The following table lists the most commonly used gamma-emitting radionuclides in nuclear medicine. The values in brackets in the column "Major energies" correspond to the total energy of disintegration. In practice, Technetium-99m, Iodine-123 and Thallium-201 are the most frequently used radionuclides today in SPECT nuclear medicine imaging modalities.

Radionuclide	Half-life	Types of rays	Major energies (in keV)	Comments
Chromium-51	27.7 d	X,γ	320	Very limited remaining interest Source: reactor
Gallium-67	3.26 d	EC γ	93 190	Imaging, but potential therapeutic use due to its Auger electron emission. Becoming less relevant Source: cyclotron
Indium-111	67.3 h	γ,EC	170 250	Nuclide used as imaging surrogate for ^{90}Y. Potential therapeutic use due to its Auger electron emission (oncology – haematology). Presently becoming less relevant Source: cyclotron

Iodine-123	13.2 h	EC, γ	160	Ideal radionuclide for covalent labelling of organic molecules; potential therapeutic use due to its Auger electron emission (oncology – neurology) Source: cyclotron
Technetium-99m	6.02 h	γ	140	Most common radionuclide for diagnosis, produced on site from the Molybdenum-99/ Technetium-99m generator (oncology – cardiology)
Thallium-201	3.05 d	X,γ	170	Cardiology imaging Source: cyclotron
Xenon-133	5.24 d	β^-,γ	810	Radioactive gas for imaging (oncology – pneumology) becoming less relevant Source: reactor

EC: Electronic Capture

For SPECT imaging, ^{99m}Tc has the longest history and the highest potential and will continue to be the driver for a long time in this imaging modality. ^{123}I has also some potential, but its short half-life associated to the necessity of a nearby high energy cyclotron will continue to limit its development and maintain its high price.

2. Positron Emitters (β⁺)

The most frequently used positron emitters radionuclides in nuclear medicine are indicated in the following table. Among these radionuclides, only Fluorine-18 is currently available at an industrial level. All the others were research tools up to now, but Gallium-68 is currently being developed at high levels, and new tracers labelled with 68Ga are reaching the market. The disintegration of β^+ emitters always goes with the production of two 511 keV gamma rays, corresponding to positron annihilation (not in the table). Energy values as provided between brackets correspond to the total energy of disintegration.

Radionuclide	Half-life	Types of rays	Maximal energies (in keV)	Comments
Carbon-11	20.4 min	β^+	960	Half-life just sufficient to label an organic molecule and to inject into man immediately after labelling. Research purpose and local cyclotron production only
Copper-64	12.7 h	β^+, β^-, γ and EC	653 579	PET imaging radionuclide with high interest under development Source: cyclotron
Fluorine-18	110 min	β^+	630	Ideal and presently most frequently used radionuclide for PET imaging; however, requires proximity to dedicated cameras (oncology – haematology – neurology); Source: cyclotron
Gallium-68	68 min	β^+	1,900	Positron emitter that can be produced from a Germanium-68/Gallium-68 generator Interest strongly raising Production also possible from a cyclotron
Iodine-124	4.18 d	β^+, EC γ	2,130	Positron emitting radionuclide with a strong energy. Slowly replaced by ^{89}Zr Source: cyclotron
Nitrogen-13	10 min	β^+	1,200	Positron emitter used only in research mainly under the form of ammonium ion for cardiology Source: cyclotron

Oxygen-15	2 min	β^+	1,730	Radionuclide with a too short half-life forbidding integration in a molecule; therefore, used in the form of labelled water generated directly from the cyclotron; Cardiology and neurology
Rubidium-82	1.3 min	β^+ γ	3,350	Radionuclide obtained from a Strontium-82/ Rubidium-82 generator; used in cardiology
Yttrium-86	14.7 h	β^+	1,250	Positron emitter radionuclide used as PET imaging surrogate for ^{90}Y; currently research tool only and becoming less relevant Source: cyclotron

PET emitter radionuclides considered to be 'exotic' which could present some interest in the near future include Scandium-43 or Scandium-44. ^{18}F will continue its extension but a long list of ^{68}Ga-labeled tracers is under development, and both ^{18}F and ^{68}Ga will probably share the market for the next years. ^{64}Cu has a high potential, but it requires the installation of a network of cyclotrons; this investment will only make sense when molecules labelled with ^{67}Cu come on the market, as ^{64}Cu will become the partner imaging agent for this therapeutic radionuclide.

3. Electron Emitters (β^-)

The number of β^- emitting radionuclides is particularly important. At this stage, about a dozen elements present interesting physical characteristics. The most commonly used radionuclides are listed in the following table. The relevance of some of them is already declining (Phosphorus-32 for example), while new ones are emerging (in particular Lutetium-177). In practice, Samarium-153, Strontium-89,

and Yttrium-90 which used to be the most often used radionuclides are becoming less relevant.

Radionuclide	Half-life	Types of rays	Maximal energies (in keV)	Comments
Copper-67	61.9 h	β^- γ	390	Newcomer with high potential but still needs high investment to secure its production Source: accelerator or high energy cyclotron
Erbium-169	9.4 d	β^-	350	Radionuclide for radiosynovectomy (rheumatology); becoming less relevant at the same time access to target metal is becoming limited; Source: reactor
Holmium-166	26.8 h	β^-	1,850	Therapy (oncology) Nice profile but source (reactor) limited to a couple of countries
Iodine-131	8.02 d	β^-,EC γ	610	Diagnosis and therapy, ideal for the treatment of thyroid diseases (oncology); most commonly used therapeutic radionuclide, but to be replaced by ^{177}Lu in new approaches; Source: reactor
Lutetium-177	6.71 d	β^- γ	500	Most interesting radionuclide for the near future with almost all new therapeutic approaches (oncology) based on it; Source: reactor

Phosphorus-32	14.3 d	β^-	1,710	(hematology) Interest fading (half-life is too long) Source: reactor
Rhenium-186	3.77 d	β^-,X γ	1,080	Radionuclide for radiosynovectomy (rheumatology); becoming less relevant Source: reactor
Rhenium-188	16.9 h	β^- γ	2,120	Radionuclide for therapy produced from a Tungsten-188/Rhenium-188 generator (oncology) becoming more relevant, but limited number of new drugs under development
Samarium-153	46.3 h	β^- γ	700	Used mainly in the palliative treatment of pain linked to bone metastases (oncology); becoming less relevant Source: reactor
Strontium-89	50.5 d	β^-	1,490	Used mainly in the palliative treatment of pain linked to bone metastases (oncology) So far still a good product but single indication application: Source: reactor
Yttrium-90	64.1 h	β^-	2,280	Radionuclide produced either by irradiation in a reactor, or from a Strontium-90/Yttrium-90 generator. Radionuclide for metabolic radiotherapy (oncology – haematology) radiosynovectomy and brachytherapy becoming less relevant and in radiotherapeutics replaced by ^{177}Lu

In the past years, Lutetium-177 has gained significant relevance as worldwide availability was implemented. ^{177}Lu is replacing ^{90}Y in almost all applications, and the new drugs due to appear on the market within the next years are almost exclusively based on ^{177}Lu. As ^{166}Ho has a profile quite similar to ^{177}Lu, it makes no sense to invest in the production network for ^{166}Ho and the radionuclide that could really compete with ^{177}Lu is only ^{67}Cu. However, ^{67}Cu still needs investment in the production technology and the associated network, and it will take at least 10 years before a ^{67}Cu labelled drug reaches the market. Beta-emitting radionuclide for therapy that could present some interest in the near future include ^{188}Re because of its generator-based production and newcomers such as Scandium-47. Beta-emitters will continue their development in parallel and as complement therapy with alpha-emitters or conversion electron emitters.

4. Alpha Emitters (α)

Several teams of researchers are currently working on the development of molecules labelled with alpha emitters. In the series of the actinides, most of the radionuclides are alpha emitters, uranium and plutonium being the best known ones. Unfortunately, only very few of these radionuclides have properties conform to nuclear medicine constraints. The legislation currently in force also limits their use, and particularly their transport. So far only one product has been made commercially available, namely Radium-223 for the treatment of late-stage prostate cancer. Radium-224 used to be available in the treatment of ankylosing polyarthritis, but this drug was subsequently withdrawn from the market. The following table lists the alpha-emitting radionuclides that may be marketed within the next decades.

Radionuclide	Half-life	Types of rays	Maximal α energies (keV)	Comments
Actinium-225	10.0 d	α	5,730	Alpha-therapy; produces 4 a particles per atom during the process of disintegration. Parent isotope used in the Bismuth-213 generator (oncology – haematology) Source: cyclotron
Astatine-211	7.2 h	α	5,870	Alpha-therapy Source: cyclotron
Bismuth-212	60.6 min	α	6,090	Alpha-therapy Source: uranium chain decay
Bismuth-213	45.6 min	α, β^-	5,870	Alpha-therapy, obtained in a generator based on Actinium-225 decay
Lead-212	10.64 h	β^-, α,	6,090	Beta emitters which decays in ^{212}Bi Source: industrial ^{224}Ra/^{212}Pb generator
Radium-223	11.4 d	α	5,715 7,386	One drug on the market Source: reactor
Radium-224	3.64 d	α	5,680	Precursor of Bismuth-212 in a generator; not available on the market anymore Source: uranium chain decay

The next generation of alpha-emitters will be based in priority on ^{211}At and ^{225}Ac, whose production and chemistry are the easiest among all the above-listed radionuclides. Potential "exotic" alpha emitters labelled drugs under development could include Terbium-149 or Thorium-227.

There is an additional approach for developing therapeutics that is based on conversion or Auger electrons emissions. These electrons are not ejected from the nucleus after transformation of a neutron like with beta emitters, but they come from the electron clouds as a reaction of effects in the nucleus. As a consequence, it is a particle similar to the beta emission that has an ionization potential closer to an alpha-emitter. They are only efficient at a very short distance; still, they show a very high efficacy level, but should be located very close to the DNA of a cell. With the exception of some tests performed with Copper-64 in brain tumours, the conversion electron emission is at a very early research stage. Radionuclides which are useful with this property have been described in previous tables, as most of them are also positron or beta emitters (^{111}In, ^{125}I, ^{64}Cu) with the exception of a newcomer, Tin-117m (^{117m}Sn, half-life 13.6 days, EC 140 keV, also a gamma emitter at 159 keV)

5. Radionuclides for Brachytherapy and External Radiotherapy

The following radionuclides are used in external radiotherapy, internal radiotherapy (temporary implants), and brachytherapy (permanent implants). Definitely out of the scope of nuclear medicine, they are usually characterized by long half-lives and used as a source of radiation. In consequence, such radionuclides must not be injected.

Radionuclide	Half-life	Types of rays	Maximal energies (keV)	Comments
Californium-252	2.6 years	n	6,110	Source of neutrons for the techniques of therapy based on neutron capture
Caesium-131	9.7 d	γ, CE	34	Source of irradiation – sterilization

Caesium-137	30 years	β^-,γ	1,170	Source of external beam radiotherapy
Cobalt-60	5.26 years	β^- γ	320 1,170 1,330	Source of external beam radiotherapy (cobalto-therapy)
Iodine-125	59.9 d	γ. CE, X	27	Isotope used in biomedical analyses (radio-immuno-analysis) of blood and urine. Used also in permanent implants for prostate cancer therapy (seeds)
Iridium-192	73.83 d	β^- γ,X	670 320	Implants used in the form of metallic wires – brachytherapy – breast cancer
Palladium-103	16.99 d	X, γ	20	Radioactive implants for the treatment of prostate cancer (brachytherapy – seeds)

This list should also include Yttrium-90 and Holmium-166 (previously described as beta emitters) which found an interesting application in the form of labelled microspheres used in liver cancer as brachytherapy devices.

6. Other Radionuclides

This last table lists various isotopes that are of some interest to the industry and sometimes also to medicine, but that have nothing whatsoever to do with radiopharmaceuticals. Some of them are filiation isotopes which can be mentioned in issues related to the nuclear waste management in nuclear medicine departments. All of these radionuclides are listed for information purposes, and their properties can be compared to those of the other radionuclides (energy and half-life).

Radionuclide	Half-life	Types of rays	Major energies (keV)	Comments
Carbon-14	5,730 years	β^-	160	Used in object dating; sometimes used to study animal metabolism, and more rarely, human metabolism; present in all carbon containing material, and hence in human food
Germanium-68	271 d	EC	106	Parent nuclide in the $^{68}Ge/^{68}Ga$ generator Source: cyclotron
Hydrogen-3 (Tritium)	12.3 years	β^-	19	Present in nature in trace amounts, therefore also in the human body. Mainly used in research as a biological tracer
Lutetium-177m	160 d	β^-	153	Long half-life waste in the ^{177}Lu quality produced by direct irradiation of ^{176}Lu
Molybdenum-99	2.75 d	β^- γ	1,370 740	Radionuclide that cannot be used directly as a tracer, but very important as a source of Technetium-99m in the $^{99}Mo/^{99m}Tc$ generator Source: reactor
Strontium-90	28.5 years	β^-	550	Precursor of Yttrium-90 in the $^{90}Sr/^{90}Y$ generator Source: reactor
Technetium-99	214,000 years	β^-	290	Decay product of Technetium-99m. Technetium does not exist in the form of a stable isotope
Tungsten-188	69.4 d	γ,β^-	350	Precursor of Rhenium 188

Uranium-235	710 million years	α	4,400	Natural source
Uranium-238	4.5 billion years	α	4,200	Natural source

SUMMARY

In this chapter we have learned that a **radionuclide** is a substance that degrades in a very constant manner over time, and emits one or several **radiations.** This degradation or **decay** is defined by a constant, the **period** (or **half-life**) corresponding to the time it takes for half of the remaining substance to disappear. This half-life is specific for each radionuclide.

The type of emitted radiation is also specific for each radionuclide. There are four types of radiation which are of interest to nuclear medicine: for diagnosis purposes, **gamma rays** (γ) and **beta plus (or positron) emissions** (β^+) have respectively led to the development of the imaging modalities **SPECT** (Single Photon Emission Computed Tomography) and **PET** (Positron Emission Tomography).

Beta minus (β^-) or **alpha** (α) radiations are used in metabolic radiotherapy.

The amount of radioactivity emitted by a radionuclide is expressed in **becquerels (Bq),** one Becquerel corresponding to the degradation of one atom per second. The amount of energy transferred by this radiation is expressed in **grays (Gy)**, while the equivalent absorbed dose by a tissue is given in **sieverts (Sv).**

Most of the matter existing on Earth, including living matter and hence the human body, contain radioactive substances.

The total amount of natural radioactivity absorbed by one man over the course of a single year corresponds in average to 2.4 mSv (but can vary between 1 and 260 mSv depending on the surrounding natural radioactivity). This average value becomes a

reference when compared to the radioactive doses received from non-natural sources.

Among all the radionuclides with potential in nuclear medicine, we shall remember the currently most used ones: Iodine-123 and Technetium-99m as γ emitters, Fluorine-18 and Gallium-68 as β^+ emitters, Iodine-131 and Lutetium-177 as β^- emitters. Newcomers in the alpha-emitting series will include Astatine-211 and Actinium-225.

4

SPECT Imaging: Gamma Ray Imaging

Nuclear medicine is above all a functional imaging tool. Monitoring the distribution of radioactive substances injected into patient provides physicians with information that is not accessible by other means in specialties as diverse as oncology, hematology, cardiology, or rheumatology. In fact, almost every medical expertise can benefit from this imaging modality. Additionally, it is now clearly demonstrated that the ionizing properties of certain radionuclides can also be of unique benefit to the patient as therapeutics. This aspect will be described in detail in *Chapter 6*.

For almost half a century, quality images could only be obtained with gamma radiation, and most radiopharmaceutical products were developed on the basis of gamma-emitting radionuclides associated with the imaging tools available for this type of radiation. Positron sources have been developed in the course of the last three decades further to the invention of dedicated cameras, and above all of improved user-friendly methods of producing β^+ radionuclide sources. We will take a closer look at this fast-developing technology later in this book.

IMAGING METHODS

High-quality anatomical or morphological images (the shape and size of an organ) may be obtained via three different methods, besides scintigraphy: radiology (X-rays), ultrasound (US), and magnetic resonance imaging (MRI). The four techniques are based on completely different principles and, as a result, diverse and often complementary information can be obtained. These imaging techniques are said to be non-invasive and do not require anaesthesia nor hospitalisation. They provide much more than a simple three-dimensional picture of tissue and organs which are not visible from the outside.

Radiology and X-rays

The use of X-rays for obtaining medical images is the oldest known method. An X-ray is an electromagnetic wave of the same type as light waves but with a higher energy level, thus capable of travelling through matter to some extent. The technique is based on the capacity of matter to attenuate an external beam of X-rays depending on whether it is solid, liquid, or gaseous. Therefore, organs will allow radiation to pass through them according to their density, thickness, and constitution. The intensity of the rays was for a long time measured on photographic film, but now specific detectors acquire the information on an electronic data basis. It is possible to render certain areas opaque by injecting a contrast product into the cavities (digestive system for example), thus holding back the X-rays.

Initial applications focused on organs and tissues presenting a different coefficient of absorption. Reference should be made to the most common application, namely displaying the skeleton and revealing every defect and malformation. Image quality improved along with improved equipment and detection methods. Today's images are nothing like those obtained in the late 50s. Not only have the resolution and quality much improved, but above all, the quantity of radiation necessary to obtain an image has considerably decreased, thereby greatly reducing the doses absorbed by both the patient and

the operator. A factor-of-20 gain has been achieved in the doses received during a simple lung X-ray over the past 40 years.

Even if most of the images still look like the original silver grey, flat and rigid document, the technology was revolutionized by the advent of digital imaging. Thanks to the improved calculation power in computers, the time needed to process images has been considerably reduced.

Tomography (from the Greek *tomein* meaning "to slice"), has improved the image quality. Computed tomography uses an X-ray source which revolves around the body to give a sectional image. A helicoidal or spiral scanner combines this rotation with an axial movement, allowing for a complete three-dimensional image of the body to be taken in 20 seconds with the latest generation devices. In the case of a three-dimensional scan of the lungs, patients only have to hold their breath for 7 to 8 seconds. The matrix detectors that equip these devices enable tumour and inflammatory processes to be monitored in every body organ. Once the data have been acquired and computed, the software equipping these tools gives the radiologist the option of navigating from one organ to another, and of isolating a particular element in order to focus on the element of interest. Then, the entire data, including the images, can be sent to a colleague for confirmation or additional expertise with a simple click of the mouse.

At the same time, contrast agents used in radiology have made considerable progress, adding to the quality and resolution of the images. As soon as it was understood that the density of the matter crossed by the ray was linked to the opacity of the image, it was also understood that a different image could be taken of an irrigated region filled with a contrast agent. Such contrast medium needs to be neutral, therefore non-toxic, and has to be eliminated rapidly from the body after imaging. Blood circulation images became the first applications, followed by liver or bile function images. Contrast agents, often based on iodine or barium, have now become unavoidable as they give an extremely precise display of certain anatomic details – such as very small vessels for example.

Radiology is more particularly used in orthopaedics, rheumatology, and orthodontics. It is also very informative in pneumology (preventive radiology of the lungs or where there is a suspicion of lung cancer), and in oncology (mammography, preventive examination for the detection of breast cancer). Contrast radiography is more specifically used in gastroenterology (stomach, liver, gallbladder, intestines). Scanners are ideal to obtain three-dimensional images (cardiovascular system, detection of tumours, analysis of organs before surgery, etc.).

A patient who has just been subject to a radiological examination is not radioactive, even if X-rays are a form of radioactivity. Outside the field, the effect of the radiation disappears. Progress in these last years has been effectively aimed at reducing both the time taken to acquire the image and the dose necessary for this acquisition, while maintaining – and even improving – quality. But whatever the technology supporting X-ray detection may become, this method will remain a diagnosis procedure and will presumably be limited to anatomical imaging.

Ultrasounds

Ultrasounds are waves that are imperceptible to the human ear, but which retain such properties as reverberation (echo) and matter absorption (attenuation). By taking advantage of these two characteristics and the properties of tissue subject to ultrasound, it has been possible to develop a tool capable of measuring and analysing the nature of its reflection, according to the tissue through which it has travelled and off which it has bounced. Measurement of the time required for the wave to be detected also permits the distance travelled to be calculated. The ultrasound technique permits the restitution, thanks to appropriate software, of the shape of organs reached by the beam. The technique has become well-known in monitoring pregnancy, but it has also been developed in other fields ranging from cardiology to oncology. Doppler ultrasound enables fluid flow (blood in particular) and tissue irrigation to be analysed.

Image definition has been very clearly improved, and colours as well as animated sequences have made their appearance. Several contrast agents, composed of micro air bubbles trapped in biodegradable substances, have been developed. As ultrasounds are completely reflected by air, these products allow for images of cavities to be taken in the same way as contrast agents are used in radiology. The resolution of traditional devices seems low, but the information obtained is sufficient for most analysis, thereby avoiding investment in a more powerful device. The latest, top-of-the-range tools offer a resolution smaller than a tenth of a millimetre and are used more particularly in eye and skin analysis. Some teams of researchers are looking for contrast agents attached to vectors targeting a specific mechanism, but are far from finding an agent that can be marketed.

Due to the opacity of areas containing air, the lungs, digestive tract, and bones cannot be analysed using ultrasounds. This technique is particularly useful in cardiology (heart and vessels, despite difficulties of interpretation in cases where the ribs create interferences), gastroenterology (liver, gallbladder, kidneys), urology (genitals, bladder), and of course, obstetrics.

A patient who has just been subject to an ultrasound examination is not radioactive. But as with X-rays, ultrasounds can presently only be used as a diagnosis procedure limited to anatomical imaging. However, new technology able to focus ultrasounds on a single point generates a strong disruptive signal that can be used for destroying at a distance. Associated to a technology that precisely controls the positioning of this focal point, it becomes possible to use these waves in the treatment of cancers (brain cancers in particular).

Magnetic Resonance Imaging

When creating the name Magnetic Resonance Imaging (MRI) physicians wanted to avoid using a word that might frighten patients, the true name of the technology being Nuclear Magnetic Resonance. Nuclear physicians, who have no connection with MRI, have raised this same

physicians, who have no connection with MRI, have raised this same question, but could only suggest "Molecular Imaging" which is not specific for tracer-based imaging. On the other hand, no consideration of radioactivity comes into the MRI concept, and it only refers to magnetism and magnetic field measurement. Subject to a magnetic field of a defined intensity, the nuclei of certain atoms, themselves conceivable as mini-magnets, align to this field. By subjecting these atoms to a wave of very short radio frequency and specific to this atom, one of their parameters can be changed: their direction of rotation, namely their spin. They enter into resonance with this wave, that is to say, they start to vibrate at the same frequency. When this external radiofrequency is switched off, their return to a normal state is expressed by the restitution of this energy in the form of a signal which can be captured and measured. The origin of the signal can be found practically atom by atom as these are located in space. In organic tissue, hydrogen is the most common atom with this property. Hydrogen is also the most common atom in human tissue because it is the main element in water and fats, making up almost nine tenths of our body weight. Therefore, three-dimensional displays of the body density of water, fats, and other organic matter containing hydrogen can be obtained with MRI. As this density differs from one organ to another, the outline of these elements is easily obtained with a precision of a few millimetres. Much more powerful tools are currently being developed that will give a resolution of under a tenth of a millimetre. As the technique is still costly, it is preferable to use traditional radiological methods to display a broken arm, and the result is just as convincing.

Hydrogen is by far not the only element that could be used in MRI, but the density of its atoms remains the greatest. Iron is an interesting element on the other hand. It is well known to physicians, above all because the presence of particles or pieces of metal (implants, prostheses), even powders and iron oxides (contained in makeup products) can lead to a major distortion of the final image, thereby impeding its interpretation.

Contrast agents developed in this field are based on the properties of gadolinium, another metal with interesting magnetic properties which gives specific organ contrast when grafted onto certain substances.
Although highly sensitive, the modality cannot reach the cellular and biological level like SPECT and PET, and therefore functional analysis is possible in some very specific cases – such as intra and inter-tissue liquid displacements like brain irrigation or heart functioning monitoring.
If MRI was not as expensive and was more widely available, it would easily replace most of the above-described CT techniques. The MRI acquisition time also remains the longest among all the imaging modalities. For the time being, MRI is preferred for examinations where a diagnosis seems more difficult (soft tissue such as muscles, tendons, brain, tumours) or in indications for which this method is much more effective or unique (neurology, ophthalmology, cardiovascular, endocrinology, oncology, etc.).
A patient who has just undergone an MRI examination is no more radioactive than a patient who has received ultrasounds – nor are they magnetised or magnetic. But as with X-rays and ultrasound, applications of MRI are limited to diagnosis procedures, mainly in anatomical imaging. In this field as well, it is expected that improved contrast agents can be developed for functional imaging with a main use in oncology, but the sensitivity of a radiopharmaceutical remains technically inaccessible.

A Combination of Techniques

The three procedures described above are, and will long remain, limited to anatomical evaluation. Organs and tissues can be very easily identified, their conformation checked, and modifications of their shape monitored over time, in particular regarding growth or reconstitution, but physicians are not capable of finding out if the tissue being studied is functioning optimally. No, or very limited, information on the mechanisms controlling the cells is available with these modalities. Only a method which could imitate these cell mechanisms

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could give an answer. Nuclear medicine imaging remains the only method capable of carrying out both a morphological analysis of the organs and a functional tissue analysis. Its measurement precision remains an advantage over the first three methods. Physicians have understood this, and they also know that the four methods are complementary, each providing information at a different level. Hybrid technologies combining PET and CT, SPECT and CT, or PET and MRI have appeared on the market over the past 15 years. These combined technologies have shown such major advantages that, nowadays, hybrid PET/CT cameras are the only ones being used, while the development of SPECT/CT and PET/MR remains limited by the high price of such equipment.

I. NUCLEAR MEDICINE IMAGING METHODS

Nuclear imaging uses either salts and radioactive complexes, or traditional pharmaceutical molecules (drugs), or biochemical molecules (hormones, antibodies) that we will call vectors, to which a radionuclide (label) is grafted. These molecules are introduced into the organism by injection, ingestion, or inhalation, and the physician can follow their distribution with appropriate detectors (cameras) thanks to the radioactive signal emitted by the radioisotope (scintigraphy). The words *tracer* or *radiotracer* are used to define these radiopharmaceutical molecules, which are used for generating the diagnosis images.

The whole structure of the molecule must be designed in such a way to ensure that the radioisotope does not break free from its vector through a natural biological process (rapid metabolism), or that it is not eliminated too quickly from the organism. This entity participates in the natural cell mechanism and allows for it to be monitored. Therefore, for nuclear medicine diagnosis is above all based on functional exploration. The biodistribution of the product and its associated image change over the course of time, until the

tracer is fully eliminated from the body. This technique cannot be used to obtain images of an organ that has been damaged, since the radioactive molecule must be able to participate in the cells' biological mechanisms. It could for example easily be used to distinguish the brain of a living person from that of someone who is is clinically dead. This differentiation is not possible with other imaging techniques. MRI, X-rays, and ultrasound will still provide almost the same image of the state or shape of a body or organ – in this case the brain – whether the individual is alive or dead. Images of an organ that is no longer functioning will be totally different when obtained with a radioisotopic tracer, even if the said organ is artificially irrigated.

The quantities administered are extremely low, yet sufficient to be detected. The great strength of imaging in nuclear medicine lies in this sensitivity. Gamma cameras are able to detect minute tracer quantities – less than a billionth of a gram – while X-rays require a local concentration of several milligrams, and of several grams for MRIs, to produce a contrast. The tracer quantities required for diagnosis studies in nuclear medicine are so low that although they participate in the normal biological mechanism of a cell, they do not interfere with it and show no pharmacological activity. The quantity of radioactive iodine (Iodine-123 or Iodine-131) used during thyroid scintigraphy remains over a thousand times smaller than the dose of stable iodine (Iodine-127) absorbed with the daily food intake.

By contrast, this high degree of sensitivity is accompanied by poor spatial resolution, that is to say it is difficult – quasi-impossible even – to obtain clear images and visible details. The shape and size of small lesions cannot be observed precisely, and as of now the method does not allow two neighbouring lesions of less than a centimetre in size to be distinguished. However, even very small tumours will remain visible if the contrast is sufficient, in other words if there is not too much background noise, or if the vector is truly specific to the targeted tumour and does not accumulate in surrounding tissues. This physical limit explains why the technique is not used

routinely for certain applications, such as in scinti-mammography (breast cancer). From the point of view of physical properties, i.e. at the detectors' level, the tool has doubtless reached its limits with resolutions of approx. 3 to 5 mm. The development of the hybrid SPECT/CT technique now enables physicians to break through this limit, since the location of the source has become extremely precise even though the image of the source remains less than clear. Another great step forward needs to be made by improving the specificity of the vectors, that is to say, their capacity to target a tumour while remaining at a very low concentration level in healthy cells.

The radioisotopes used in medical nuclear imaging must have a relatively short half-life. As a result, the patient's own radioactivity level decreases rapidly over time. When this level of radioactivity has lowered to within public safety standards, patients can leave the hospital. In fact, in most diagnosis uses, this safety threshold is never even exceeded – meaning that no hospitalization or confinement to a protected hospital department is required for imaging. It should be remembered that the level of radioactivity is reduced by a factor of about 1,000 after a period of 10 half-lives, and that radioactive emissions are 100 times lower at 1 m than at 10 cm. Therefore, spending less time with, and staying further away from, radioactive patients considerably reduce exposure risks. This rule is especially valid for medical staff working closely with patients. The emitted doses following a simple injection of radioactive imaging substances are of no consequence for the patient, and are therefore of even less consequence for the patient's friends and family.

1. Scintigraphy

Scintigraphy covers techniques analysing γ rays that are transformed into a flat image similar to an X-ray plate. The radiation comes from the substance injected into the patient and which has concentrated in certain tissues. Therefore, these tissues become themselves the source of this radiation, which is recorded on the photographic plate or

specific detectors. An external radiation source that crosses the whole patient body is required during the period of image acquisition when using X-ray imaging.

Let us take a quick look at the diseases that can benefit from scintigraphy. Almost all organs can be investigated by this technique, and above all their functions can be checked without the need for a surgical operation or biopsy. This method is said to be non-invasive.

One of the most frequently performed investigations is bone scintigraphy. A whole body image of a patient suffering from bone pain provides information on bone function. Scintigraphy will detect any increase in bone metabolism corresponding to a lesion. Almost all solid cancers eventually form metastases which systematically develop on the bones. Bone scintigraphy enables practitioners to search for these bone metastases in an effective manner.

The heart is another organ that benefits from advances in this technology. When heart discomfort is experienced, or in almost every chest pain case leading to a suspicion of heart failure, the patient undergoes a test that frequently requires myocardial perfusion scintigraphy. This tool is used to test the heart muscle's condition and irrigation – in other words, the heart pump's functioning. The technique is based on monitoring the heart's biological mechanisms, and does not dwell on the shape of the organ. In consequence, myocardial perfusion scintigraphy images show very little resemblance to a heart.

The kidneys also benefit from the properties of specific radio-labelled vectors. Renal scintigraphy provides the urologist with important information concerning blood exchanges and the organ's functionality. Patients suffering from hypertension and diabetes as well as patients likely to suffer from kidney stones are subject to such routine tests.

Scintigraphic imaging of the thyroid is the most widely known specific method due to the systematic accumulation in this tissue

of any iodine absorbed. Thyroid scintigraphy is used to screen for abnormal functioning of the thyroid gland (hyper- or hypo-thyroid), as well as malignant tumours of this gland. Secondary thyroid cancers accumulate iodine in the same specific manner, thus it is possible to monitor the disease's development using the same tools.

As for the brain, the tools available to date enable testing of the irrigation vessels' condition, and monitoring of diseases such as epilepsy and possibly Alzheimer's. More specific molecules for brain scintigraphy, e.g. for early detection of Parkinson's disease, have appeared on the market in recent years.

Pulmonary scintigraphy is a more particular technique. It requires the use of a radioactive gas that is inhaled, giving an overall image of every alveolus in the accessible airways. This technique is called pulmonary ventilation scintigraphy; it supplements pulmonary perfusion scintigraphy in which a lung image is obtained on the blood vessel side after injecting a radioactive substance in the blood vessels. The superimposition of these two images, which complement each other, shows the interface between the oxygen in the air and the blood system in the lungs. For a patient suffering from a pulmonary embolism, an incomplete image pinpoints the areas no longer participating in the oxygenation.

Finally, nuclear medicine can provide vital indications in determining infected or inflamed areas when these are touching soft tissue or internal organs that are difficult to access. For example, this technique – very little used in Europe but gaining ground in the United States – can confirm appendicitis before an operation. This diagnosis aid helps physicians avoid post-operative legal complications, if it turns out that an operation should not have taken place.

2. The Products used in Scintigraphy

The diagnosis radiopharmaceuticals, which concentrate in the tissue to be analysed, possess particular biological, chemical, and

radiological properties. Experience gained over the last fifty years gives a better understanding of the mechanisms that favour this local concentration, thus enabling researchers to develop more specific – and therefore more effective – radiolabelled molecules.

The diagnosis effectiveness of a radiopharmaceutical is obviously linked to the specific characteristics of the vector, the non-radioactive part of the molecule, and the half-life of the isotope that is attached to it. These parameters are not sufficient however, because if this radiopharmaceutical molecule degrades before it reaches its target or leaves it with no interaction, it becomes of no use. Consequently, another parameter called the effective half-life needs to be considered which takes into account the contact time between the ligand and its target. More importantly, in addition to the knowledge of the radioisotope's decay, it is crucial to have data available concerning the time of the molecule's residence in the target cell – this is called the biological half-life. Ideally of course, we would have access to a molecule with a maximum residence time in the cell or target organ, and almost none in all other parts of the body. This is never the case. With the exception of iodine used for imaging or treating the thyroid and for which the isotope itself is the ligand, it is actually the vector which plays this important role of selectively targeting the radiopharmaceutical onto the target organ. The combination of the half-life of the isotope and the biological half-life defines the effective half-life, which itself determines the real impact of a molecule on its target.

The ideal radiopharmaceutical is defined by a high level of binding (the capacity of a molecule to attach itself to the inside or the surface of a cell, i.e. a receptor). For a specific receptor-ligand pair, most of the time, these fixation values are known. The radiochemist's main task will be to attach the radioisotope to this molecule while avoiding any disturbance to its interaction with the receptor, and therefore to its biological effectiveness.

Commercially available diagnosis radiopharmaceuticals and their indications (gamma emitters - SPECT imaging tracers)

Isotope	Chemical form of the radio-pharmaceutical	Indications
Chromium-51	Sodium chromate	*In vitro/ex vivo* labelling of red blood cells (measure of volumes, masses and survival time) – becoming less relevant
	Edetate	Renal filtration – becoming less relevant, replaced by Technetium analogues
Gallium-67	Citrate	Tumour imaging, inflammation localisation – now almost entirely replaced by PET technology
Indium-111	Chloride Pentetate (DTPA) Oxyquinoline	Labelling of peptides, proteins, and antibodies for oncology and haematology imaging – becoming less relevant
Iodine-123	Sodium iodide	Thyroid scintigraphy Labelling of molecules for imaging
	Iobenguane (MIBG)	Morphological and functional imaging of the thyroid Detection of tumours
	Ioflupane (FP-CIT)	Neurology (Parkinson disease)
	Fatty acid	Cardiac metabolism studies
Iodine-125	Iodinated human albumin	Blood volume and blood albumin renewal studies – very limited interest
Iodine-131	Sodium iodohippurate	Renal filtration studies
	Iodomethyl-norcholesterol	Adenocortical diseases
	Sodium iodide	Thyroid scintigraphy

Iron-59	Iron citrate	Gastro-intestinal absorption – becoming less relevant
Technetium-99m	Albumin (human)	Vascular and pulmonary imaging
	Bicisate	Brain imaging
	Disofenin	Evaluation of the biliary function
	Exametazime (HMPAO)	Cerebral perfusion – labelling of blood cells for the detection of infections
	Mebrofenin and Lidofenin	Liver imaging – several other tracers from the same family are also available
	Mertiatide	Renal filtration
	Octreotide	Diagnosis of neuroendocrine tumours (NET)
	Pentetate (DTPA)	Vascular cerebral, renal, and pulmonary imaging
	Pertechnetate (sodium)	Vascular, cerebral imaging; imaging of the salivary glands, the gastric tract, the lachrymal tract
	Phosphonates (medronate – oxydronate – pyrophosphate)	Bone scintigraphy – imaging of bone metastases – several tracers from the same class are available on the market
	Phytate	Liver imaging
	Tin pyrophosphate	Vascular imaging
	Sestamibi (MIBI)	Cardiac perfusion imaging – the most used tracer
	Sulphide (colloidal rhenium)	Liver imaging, sentinel node detection
	Succimer (DMSA)	Renal cortex imaging
	Technegas	Ultrafine dispersion for diagnosis of pulmonary embolism

	Tetrofosmin	Cardiac perfusion imaging
	Tilmanocept	Lymph node imaging (the most recent proprietary SPECT tracer that reached the market)
	Antibodies and peptides	Infectious sites from tumour structures imaging
Thallium-201	Chloride	Myocardial perfusion imaging (detection of infarcts, ischaemia and necroses)
Xenon-133	Xenon gas	Pulmonary and cerebral perfusion Limited interest

Abbreviations: DMSA: dimercapto succinic acid; DTPA, diethylene triamino pentaacetic acid; HMPAO, hexamethyl propylene amine oxime; FP-CIT, fluoropropyl carbomethoxy iodophenyl tropane; MIBI: methoxy isobutyl isonitrile; MIBG, metaiodo benzyl guanidine.

The table above shows that several products which were discovered and developed in the 50s and 60s are now becoming less relevant. In fact, in the meantime, new molecules with better profiles came on the market, and a kind of natural selection led to a limited number of very powerful molecules. In summary, presently and for the near future SPECT is essentially based on Technetium-99m and Iodine-123 labelled molecules which meet almost all physician needs in this domain; additionally, only Thallium-201 continues to be of some interest in myocardial perfusion imaging. Gallium-67 for example, which was of great use in the 80s and 90s, has completely disappeared; it has been replaced by the more convenient PET and ^{18}F-FDG.

II. IMAGING TOOLS

SPECT cameras are based on a specific gamma imaging tool equipped with a detection head that analyses an area up to 40×60 cm in a single pass. The gamma rays, which are actually emitted in every direction from the source, are selected by a collimator as they pass

through, and only those which are perpendicular to the detector are taken into consideration. This detector composed of a crystal sensitive to radiation (sodium iodide for example) is coupled to a photomultiplier which transforms the impact of the radiation into an electronic impulse. The impacts are analysed point by point in a planar image. The quality of a gamma camera depends on the detection crystal's sensitivity and the collimator's resolution. Moving the detection head along the length of the body gives a static planar scintigraphy image of the whole body within minutes.

The same type of equipment, used over a specific region, gives a dynamic image with which the evolution of the radiopharmaceutical's distribution through the organs can be monitored over a precise length of time. The processes of blood irrigation can also be monitored. Finally, observing the functioning of the liver or kidneys is no longer a problem when plates are taken sequentially, over a predetermined period, and with defined and regular spacing between each acquisition.

The SPECT method (Single Photon Emission Computed Tomography), i.e. the tomographic application of gamma imaging, applies the gamma camera principles to a scanner, a tool that is equivalent to the devices used in radiography.

The word Tomography stands for the mathematical procedure of reconstructing images taken by sections with the aim to transform them in first several two dimensional pictures, which when combined can provide a three-dimensional representation.

By contrast to X-ray scanning, the photon source is located in the patient himself since the radioisotope has been injected. The equipment generally uses two or three detectors which revolve around the patient, thus giving a cross-sectional image. If this data acquisition is carried out in parallel with a linear analysis, a three-dimensional image of the body is obtained. This recent improvement has been made possible thanks to the development of very powerful computers

with which these devices are equipped. The SPECT method is ideal for analysing areas that are well-defined and limited in size, such as the heart or brain.

As acquisition times remain relatively long, moving organs such as the heart are more difficult to image, or at least to interpret. As a solution to this problem, images are taken according to the heart rhythm. The period between two beats is divided into twenty or thirty sequences, and the gamma impacts recorded during each fraction of time are accumulated separately. After ten minutes, twenty or thirty different images – each corresponding to a precise fraction of the heartbeat – are recorded. By displaying them in order and in a loop, an animated sequence of the heartbeat is reconstructed. This dynamic mode technique is called gated SPECT.

This special technique may also be used when images have to be taken in the neighbourhood of the lungs, which are also subject to regular movement. The acquisition of images can be synchronised with breathing movements.

III. DETECTION OF THE SENTINEL NODE

Among the other tools used for detecting radioactivity, we will only mention per-operative probes. These permit ad hoc localisation of the concentration of a radioactive substance which was previously injected into the patient, and which has the property of accumulating specifically in the target zone. The device – the size of a large pencil – enables the surgeon to find a zone of strong radioactivity concentration using this detector. In this type of surgery, radioactivity plays the role of a label equivalent to a dye, the detection of which can only be achieved with an appropriate tool.

Two types of probes are available: scintillation detectors using a scintillation crystal (sodium iodide activated with thallium) coupled to a photomultiplier and semi-conductor probes (cadmium-tellurium) linked to a preamplifier. These probes are used for detecting and

measuring concentrations of radioactivity in tumours (colorectal cancers, breast cancers, ovarian cancers, or melanomas) and for detecting sentinel nodes (melanomas, breast).

The metastases' dissemination mechanism takes advantage of the network created by the lymphatic system. The first sets of tumour cells released by the primary tumour are initially destroyed by the macrophages present in the lymph nodes. The route taken by these cells is identical during the whole period of growth of the primary tumour. The first metastasis will install itself in the first node it meets, as soon as the macrophages are no longer capable of destroying the colonising cells. This place is called the sentinel node.

The identification and exact localisation of the sentinel node are very important as the absence of cancerous cells in this one tissue confirms that the cancer has not spread beyond the primary tumour. The metastase propagation mechanism being known for several decades, it was soon necessary to consider the surgical removal of part of the lymphatic system, starting from the tumour. In the case of breast cancer, it generally affects the lymphatic system irrigating the arm on the same side as the affected breast. This surgical ablation has been systematically practised since, and effectively prevents many cases from recurring. Unfortunately, this technique has the drawback of many side effects and high morbidity. Surgeons have therefore considered substituting limited excision of the primary tumour as well as the sentinel node.

Original detection techniques consisted of injecting a dye around the primary tumour, specifically methylene blue which, as it diffused, followed within minutes the same path as the cells released by this tumour. The surgeon only had to remove the most coloured area, detected during the operation. The technique is limited as particles are diffused too rapidly due to their small size, and also because of the non-visibility of deeply located nodes.

Radioactivity has recently come to the surgeon's aid. By replacing the dye with neutral particles the same size as the circulating cells, and

labelling them with a short-life radioisotope, it is not only possible to follow the trace of the diffusion of tumour cells, but also to mark the sentinel node depth.

In practice, the nuclear physician injects a suspension of nanoparticles at several points around the patient's tumour using a syringe (particles a few millionths of a millimetre in size) labelled with Technetium-99m (6 hours half-life). After a quarter of an hour, these particles will have diffused and will have started to accumulate in the sentinel node. Using a probe – a small radioactivity measuring device specially adapted for this technique – it is possible to detect the zone where this radioactivity has accumulated; and, taking into account the measured value, even the node depth can be estimated, thus allowing identification.

Successive surgical ablation of the tumour and then of the node can be carried out the next day, once the radioactivity has decayed.

The formation of a metastasis is determined with the histopathological analysis of the sentinel node. A negative result means the cancer has not spread. A positive result indicates the need for additional examinations and regular monitoring in order to decide if more radical therapy is required.

The technique has proven to be equally effective in the treatment of melanomas, which have the particular characteristic of forming their first metastasis in sites located several tens of centimetres from the initial tumour.

SUMMARY

Nuclear imaging makes use of radioactive substances (radionuclides combined with an organic molecule, the **vector**) which, once injected into the patient, have the particularity of distributing themselves and specifically concentrating in tissues according to the type of vector on which the radionuclides are fixed. By using gamma-emitting isotopes, it will be possible to obtain a planar image of a defined zone and

make diagnose the evolution of the disease affecting this tissue. This **functional exploration** method is called **scintigraphy.**

Associated to detectors revolving around the patient and powerful computing tools, it gives cross-sectional images which, when combined together, lead to the production of three-dimensional images. This is **SPECT** technology (**Single Photon Emission Computed Tomography**).

Practically all tissues and organs have been the subject of the development of specific vectors with which, in most cases, Technetium-99m has been combined. For certain tissues – and more specifically the brain – Iodine-123 has proven to be of particular interest.

Gated SPECT is a dynamic mode image acquisition technique coupled to the movement of the heart (or lungs), with which these disruptive factors can be ignored.

Finally, local radioactivity distribution monitoring can be carried out with probes. This technique is more particularly applied in the **detection of sentinel nodes,** allowing a breast cancer tumour to be removed more efficiently, and considerably reducing the risk of a later metastasis formation.

5

PET Imaging: Positron Emission Tomography

Positron Emission Tomography (PET) uses the particular properties of beta-plus (β^+) emitters. These radionuclides are injected into the patient in the form of labelled products supposed to bind specifically to the cells from which an image is required. Positron emitters have the particular characteristic of producing two gamma photons by annihilation (*see below*). These radionuclides could therefore be used and detected with traditional spectrometry tools. However, these gamma photons have two additional useful properties: firstly, they are emitted in two opposite directions from each other, and secondly they have the same energy of 511 keV – whatever the isotope used. This technique therefore requires a suitable imaging tool and benefits from its power and specific characteristics.

With its special physical and chemical properties, Fluorine-18 was quickly identified as being the ideal radionuclide for this imaging technology, and when the industrial production of the best radiolabelled tracer – namely Fludeoxyglucose (abbreviated FDG) – became a technically easy possibility, this technology experienced a

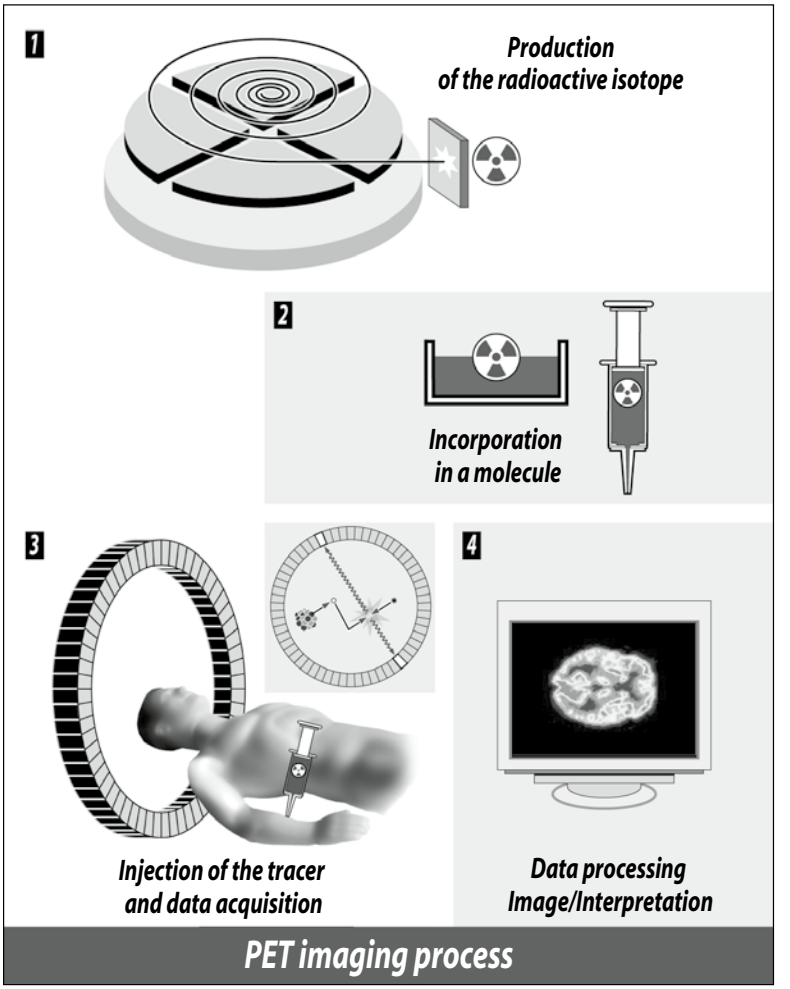

Figure 8 | As a consequence of the short half-life of Fluorine-18, PET imaging requires a four-step process that has to be performed in the shortest possible time: manufacturing of Fluorine-18 in a cyclotron (I); synthesis of the FDG molecule in a radiopharmacy unit (2); transportation of the doses to the imaging centre; injection to the patient, and acquisition of the image with a PET camera (3). The last step – which consists in processing data and reading the final images (4) – does not follow the previous steps' time constraints.

development surge. Positron emission tomography was once on the verge of overtaking SPECT techniques due to its versatility, but in the meantime SPECT progressed as well; now, both modalities are evolving in parallel without the predominance of any of them as initially expected.

In the following, PET complexity is described through the preparation process of FDG from the first step of producing Fluorine-18 up to the imaging process.

I. THE IMAGING PRINCIPLE

Beta-plus radiation (β^+) is an emission of positively charged electrons, not photons but a form of antimatter. The positrons are particularly unstable, and as soon as they meet electrons (the negatively charged entities), they self-destruct (called the annihilation process) and emit two photons which travel away from each other in strictly opposite directions with an energy of 511 keV. By placing suitable detectors on both sides of the emission site linked with computers of sufficient power, it is possible to locate the point of origin of the collision between the electron and the positron. Imaging analysis techniques combined with recording data in successive slices (tomography) enables the creation of two-dimensional – even three-dimensional – images. This is the principle of the Positron Emission Tomography modality, or more simply PET.

Unfortunately, the positron may travel a distance of several millimetres from its ejection point before encountering an electron. The distance is proportional to the energy of the emitted positron, and is different from one positron emitter to another. The final image, corresponding to the sum of the points of impact, will give the statistical distribution of these annihilation points – and not the distribution of the positron emission's points of origin. That few-millimetre difference from the actual origin of the β^+ signal also

expresses the insurmountable resolution limit, and therefore the limit of the method's image quality. This resolution of a few millimetres is nevertheless considered as excellent due to the specific nature of the vectors used. Certain micro-metastases – that is to say, metastases and tumours approx. 3 to 5 mm in diameter – still remain visible due to the high level of contrast with the background noise, but their actual size cannot be evaluated. This property of imaging very small zones is not linked to the radioisotope, but to the specific characteristics of the vector on which this element is grafted.

More precision in terms of analysing the gamma photons emitted in PET has been obtained in the later years with the introduction of the time-of-flight technology. Detectors located at opposite sites from the emission point will be hit by the two photons simultaneously if the emission pointed is centred. If there is a possibility to measure the slight difference between the two impacts, then it will also be possible to be more precise about the emission point on this axis. Knowing that the two photons are travelling almost at the speed of light, the difference of time to be measured remains below the nanosecond. Nowadays, electronic measurement tool precision can locate the emission source to a segment of less than 30 cm along this axis, thereby tremendously increasing the measure precision.

Several β^+ radionuclide emitters have been used, but none has succeeded so far in unseating Fluorine-18, a versatile element by virtue of both its radiological and physical-chemical properties. Very recently Gallium-68 appeared to be an alternative, but the first tracer labelled with this radionuclide only appeared on the market in 2016. A few other positron-emitting radionuclides are under development, among which Copper-64 or Zirconium-89 which could show some advantages either due to their more convenient chemistry or to their longer half-life allowing to follow different biological mechanisms.

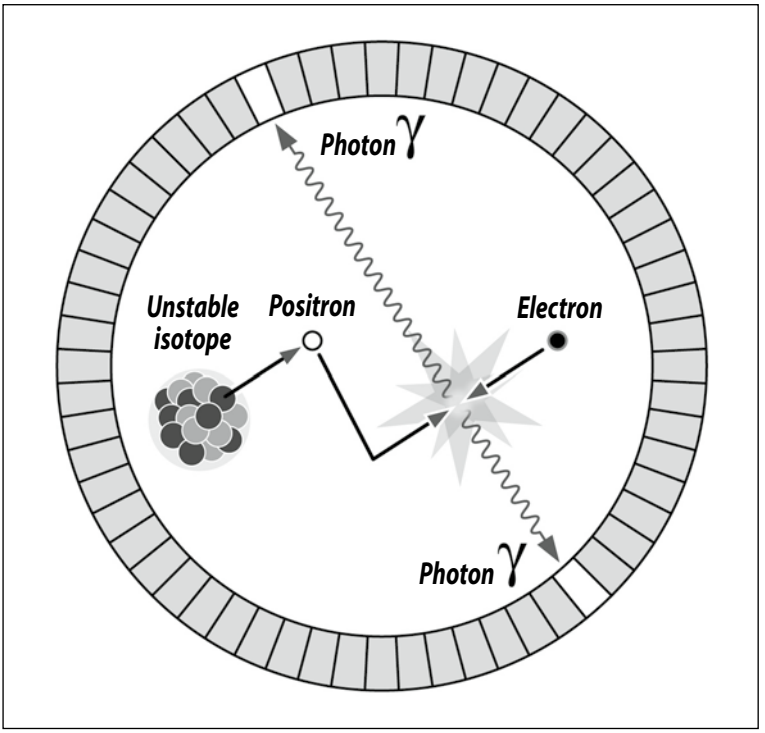

Figure 9 | Diagram of the positron emission and of the detection of both gamma photons generated by the annihilation process. Detectors are placed to form a crown shape around the central source in order to detect a maximum of double photon emissions in a same plane.

II. THE RADIATION SOURCE

Fluorine-18 belongs to the halogen family and is an extremely electronegative atom. It has the particular characteristic of being able to form a very stable covalent (strong) bond with carbon, unlike the other halogens – and particularly unlike the labile (unstable) iodine atom. Due to this advantage, it does not require ligands as for the cumbersome metal coordination chemistry. Because of its very low atomic volume – less than two times greater than hydrogen – fluorine

can easily replace other atoms in the active molecule without radically interfering with the biological properties of these substances.

From the point of view of its physical-chemical properties, fluorine is an ideal candidate for labelling imaging molecules. Unfortunately, it has a half-life of just 108 minutes. This unusual property is both an advantage and a disadvantage. On the one hand, the short half-life promotes rapid elimination and low waste accumulation impact. The patient also remains in limited contact with the radioactivity. On the other hand, the time allocated to its manufacture, synthesis, analysis, logistics, and imaging procedures must be adapted to this severe constraint.

Fluorine-18 is a pure β^+ emitter producing indirectly two 511 keV photons, that is to say without any harmful secondary radiation. This radioisotope can only be produced with a cyclotron by bombarding with a proton beam a target containing Oxygen-18 enriched water, a stable (i.e. non-radioactive) isotope of oxygen present at 0.2% in nature. This nuclear reaction transforms Oxygen-18 in Fluorine-18 with concomitant emission of neutrons. The automated method of purification on exiting the cyclotron enables this isotope to be obtained in a form free from any radionuclidic impurity that may have been formed at the same time. The resulting aqueous solution contains a very dilute form of active sodium fluoride. The chemistry developed around this isotope led to the improvement of the synthesis process of fluorinated organic molecules, essentially by nucleophilic substitution reactions with high yields. Any general synthesis method of quantitative fluorine introduction at low temperature without generating toxic by-products (or that are easily separable) would greatly improve this technology.

As a matter of interest, it should be remembered that other radionuclide positron emitters – in particular Carbon-11 – can be used in PET on specifically labelled molecules, but none has given rise to the development of a commercial product because of its shorter half-life (20 minutes).

The recent development of Gallium-labelled tracers opens new perspectives. Despite its short half-life (only 68 minutes), Gallium-68 can be grafted to a molecule the same way as Technetium-99m is used to label SPECT imaging agents. On top of this, and similarly to Technetium, Gallium-68 is easily produced with a generator and does not require this complex structure and network of cyclotrons that has been developed over the years for Fluorine-18. It seems that Gallium-68 is now opening a new era in PET imaging, but it will certainly not completely replace Fluorine-18. For example, so far radiochemists have not been able to develop a Gallium-68 equivalent of FDG.

III. THE LABELLED PRODUCT: FLUDEOXYGLUCOSE

Cancerous cells are avid for glucose; they consume more of it than normal cells. Labelling glucose with a radionuclide helps distinguish between sugar-consuming cells and their neighbours. [^{18}F] fludeoxyglucose ([^{18}F]-fluoro-2-deoxy-D-glucose) – better known as FDG – is a sugar, in which one of the hydroxyl groups (alcohol function) has been substituted by a Fluorine-18 atom. This substitution has been carried out in such a way that during the step of ingestion by the cell, the molecule is not only still recognised by it as a sugar, but it also undergoes an initial metabolic transformation (phosphorylation) which prevents it from leaving this cell again. The normal sugar is supposed to follow a second phosphorylation step which cannot take place with FDG as the reaction site is occupied by fluorine. The molecule remains trapped in this cell in the same way as all the other identical molecules which have been assimilated, creating a radiolabelled substance accumulation and therefore providing an increasingly strong radioactive signal. Certain tumour cells can take up to 30 times more sugar than their healthy neighbour cells, allowing a strong contrast in terms of radioactive signal.

The remainder of the FDG not consumed by the cells is very quickly eliminated via the urinary tract. The fluorine trapped in the cells disintegrates rapidly. According to this isotope's rapid decay rate, only less than a thousandth of the initial radioactivity dose can be detected in the body 20 hours after the injection.

FDG is injected intravenously with a dose of about 350 MBq. All the glucose consuming cells – and particularly all active cells – will trap this molecule: besides cells in the course of rapid growth and proliferation – including tumours and their metastases in particular – the brain and the heart can also be distinguished, thus opening up other possibilities for imaging. Muscle cells – which also consume glucose – will be less visible if the injection is preceded by a short period of rest for the patient.

First discovered in the 70s, FDG has been widely used on patients in the US since the end of the 80s. Its first official release with a European marketing authorisation dates from November 1998 in France; it was also used occasionally and for clinical research purposes by a few other research centres with access to a cyclotron. A number of other countries – Germany and Belgium in particular – had already been using this technology in hospitals for ten years. Since obtaining this marketing authorisation and enjoying increased support from several governments, a network of cyclotrons, combined with automated FDG production units, has been set up.

Nevertheless, to date and although numerous fluorinated molecules have been synthesised, FDG remains the only substance available on the greater scale required to meet the needs of PET technology. This will dramatically change before 2020.

IV. PRODUCTION AND EQUIPMENT

FDG production requires full control of the production of Fluorine-18, its purification, its use via an automated technique in the active molecule's synthesis and, finally, the quality control of the

final product before distribution. All these operations must be carried out within a few hours so as to lose only the minimum of active matter. Remember that the amount of product is reduced by half every two hours (the Fluorine-18 half-life lasts 110 minutes). Taking into consideration the requirement to inject the molecule into the patient as quickly as possible after its synthesis, no better solution has been found than to locate the isotope and labelled molecule's manufacturing close to the customer sites. Production units equipped with a cyclotron are built at strategic locations which allow coverage of potential users. Cameras need to be distributed less than 3 or 4 hours away in terms of distance, independently of the transportation means used. Beyond this time period, the amount of matter lost during the transport becomes too great, and the cost of doses as well as that of transport increase proportionally.

Every hour, a little more than one patient can be evaluated with each camera. Newer camera models can scan up to three patients in that same time. Each production unit – with its cyclotron – has the status of a pharmaceutical establishment and must follow current pharmaceutical manufacturing practices. They are managed by a head of compliance pharmacist who guarantees the delivered products' pharmaceutical quality.

Given the funding required for the devices and their infrastructure, the number of cyclotrons is set to stabilise very quickly at the level of 5 million euros. The number of patients to benefit from this technology in the future will depend essentially on the number of cameras available. New hospital equipment plans allowing major centres to make investments in this field actually fixed the average rate at one camera per million inhabitants. As an example, France – one of the most advanced European country in terms of industrial centres – first approved 60 PET cameras that could be supplied by about 10 cyclotrons. This figure was revised upwards several times; by 2017 in this country, more than 130 cameras were deployed, and 25 cyclotrons installed. It is probable that the number of cameras will

be further increased, considering the new applications this technique offers in oncology, haematology, cardiology, and neurology. The other European countries – which were lagging behind Germany and Belgium, both countries having developed PET on the basis of academic centres – have in the meantime grown, and the most developed countries have reached a similar equipment ratio. With the exception of the United States, over-equipped, and Russia and China, now starting investment in this technology, most developed countries have reached a fair level of equipment.

More than a thousand cyclotrons have been installed all over the world to produce Fluorine-18, and they are associated to about 5,500 dedicated PET cameras. However, globally, the SPECT equipment network is still three times stronger than that of the PET, and some remote places – including most of the smaller islands or under-developed countries – still have no access to the PET modality.

Given the technology's evolution, new equipment installed mainly consists of hybrid systems combining Positron Emission Tomography with Computerized Tomography X-ray cameras. These tools, also known as PET/CT, were invented in 2000 and have been marketed since 2002. They allow superimposed images from both procedures to be obtained, and thus pinpoint the observed elements with much greater precision.

V. APPLICATIONS IN CANCEROLOGY

The official indications for FDG as described in the European marketing authorisation dossiers cover the following areas: FDG can be used in the characterisation of isolated pulmonary nodules, and in the diagnosis of metastatic cervical adenopathy of unknown origin. It serves for the evaluation of primary pulmonary cancers – including the detection of remote lung metastases, the evaluation of head and neck tumours including assistance in guided biopsy, as well as recurrent colorectal cancer tumours, lymphoma and malignant melanoma. As

a means of monitoring therapeutic response, it is used for head and neck cancers and malignant lymphoma. Finally, in case of reasonable suspicion it is used to detect recurrences of head and neck cancers, primary lung cancer, colorectal cancer, malignant lymphoma, and malignant melanoma.

In reality, due to its universal nature, FDG is capable of detecting the appearance of tumour or metastatic cancerous cells for almost any cancer said to be a "solid cancer". Nevertheless, a demonstration of its effectiveness has not yet been carried out in all cases and other, less costly techniques may provide equivalent information. In particular, it serves for detecting breast cancer, and even helps its prevention, but other effective detection methods can faster confirm diagnosis.

FDG becomes useful when a tumour is suspected, or when a clear diagnosis cannot be obtained with more traditional methods due to a lack of suitable tumour markers – or because the zone being considered is difficult to access.

Beyond FDG which is a tumour proliferation imaging agent, numerous vectors developed on the basis of biological mechanisms and labelled with Fluorine-18 have found specific applications in oncology. Among them, only Sodium Fluoride (for bone metastasis imaging), Fluciclovine (prostate cancer imaging), Fluorocholine (prostate cancer), and Fluoroestradiol (breast cancer) obtained a marketing authorization. On the other hand, a series of fluorinated tracers for very specific indications are generics, and will probably remain research tools without official marketing authorization. Despite their diagnosis potential, the use of these molecules remains mostly restricted to clinical research due to their high cost, their low return on investment (and hence the low interest of investors), and the complexity of their transformation into medicines approved by the medicine agencies. Most of these fluorinated tracers are only locally available.

The first Gallium-68 labelled tracer (octreotate) obtained its marketing authorization in the USA in 2016 for the Neuro-Endocrine

Tumour imaging (NET) indication. It is expected that very soon other Gallium-68 labelled tracers may come on the market, in particular for prostate cancer imaging.

VI. APPLICATIONS BEYOND ONCOLOGY

The heart and the brain also consume great amounts of glucose, and are therefore potential candidates for imaging using FDG. However, these organs show a higher level of background noise, which is often a hindrance.

FDG's cardiac applications are challenged by more traditional, and above all less costly, techniques such as SPECT scintigraphy using Technetium-99m or Thallium-201. Nevertheless, these methods also have their limits, and PET could possibly be of greater interest if FDG was confirmed to be useful in measuring myocardial viability – otherwise very difficult to determine. The use of vectors specific to cardiovascular mechanisms may open other more promising avenues, but it also means more expensive tracers are proposed on the market. In the USA, Rubidium-82, a very short half-life (1.3 minutes) PET tracer based on a generator, is developing progressively in PET cardiology, but is still limited by access to a larger number of generators.

PET has made its greatest contribution in the diagnosis of neurodegenerative diseases. Almost all the active molecules in neuronal cells can be labelled with fluorine. Unlike technetium and other metals requiring chelating groups in order to be attached to the vectors, the simple chemistry of fluorine prevents any additional biological constraints from occurring, and allows the molecules to pass the brain-blood barrier. All fluorinated derivatives retain this property quasi identically to the non-labelled vector, which enables them to access the neuronal receptors at particularly high concentrations. In this case, FDG is only of limited interest as it is not sufficiently specific. In the past five years, four molecules have

obtained marketing authorizations in most of the developed countries; These are Florbetaben, Florbetapir, and Flutemetamol – all used for imaging of neurodegenerative diseases (measurement of amyloid plaque accumulation in the brain, in particular for Alzheimer's disease), and Fluorodopa – used in Parkinson's disease. These tools are so powerful than they can predict the onset of a disease's clinical signs more than ten years in advance. Their use in AD diagnosis is currently very limited, indeed, their utility will only be high when a drug becomes available that blocks the development of the disease, with the aim to never reach the memory loss stage.

Other neuroactive molecules have been labelled with Fluorine-18 – thus allowing particular pathologies to be studied, and even brain behaviour to be observed. These vectors are called dopamine, serotonin, or benzodiazepine.

VII. POSITRON EMITTERS EVOLUTION

Today, Fluorine-18 represents more than 95% of all PET scans, and we have seen that Gallium-68 may come through within the next year, in parallel to Fluorine-18. Among other β^+ emitters produced in a cyclotron, let us mention Carbon-11 (20 minutes half-life), available in the form of carbon dioxide or methyl iodide, which could easily be integrated into an organic molecular structure were its half-life not so limited. Less than half an hour to carry out a synthesis, followed by purification and quality testing, is a very constraining time for the chemist. In fact, very few molecules are suitable for Carbon-11 incorporation, and all those developed to date will presumably remain restricted to clinical trials. Oxygen-15 is even more unusual by virtue of its half-life (2 minutes), but is nevertheless used in the form of labelled water, purified and injected directly as it comes out from the cyclotron. This technique allows physicians to obtain information on the irrigation of certain tissues and fluid exchanges. Nitrogen-13 in the form of ammonia (half-life

10 min) is also used in cardiology, but Rubidium-82 remains the most convenient.

SUMMARY

Positron emitters (β^+), generating positive electrons (anti-electrons), produce two photons as a consequence of each collision with an electron (**annihilation**). These two photons – which both have the same constant energy – are emitted in two totally opposite directions. Detectors are placed on either side of the emission point to accurately locate the origin of the source. In practice, several detectors are placed in a ring around the origin of emission.

Among the positron emitters that can be used in nuclear medicine, **Fluorine-18** – with a half-life of about two hours – has found an inestimable advantage in diagnosis medical imaging. It is through the use of the fluorinated glucose derivative, **FDG** (fludeoxyglucose), that **PET (Positron Emission Tomography)** has demonstrated its effectiveness in oncology.

In the meantime, a few other fluorinated tracers have reached the market in oncology (bone metastases, prostate cancer), and neurology (Alzheimer and Parkinson disease imaging). More recently, the first **Gallium-68** labelled tracer also obtained its marketing authorization for the imaging of neuroendocrine tumours.

Nevertheless, implementing this technology requires the creation of structures (cyclotrons, synthesis laboratories, etc.) adapted to the short half-life of Gallium-68. Furthermore, the development of the technology will depend on the investment in cameras made in the territory being considered.

Other fluorinated and gallium-labelled tracers are currently under evaluation, and will soon allow the evolution of a pathology in the course of its treatment to be diagnosed, and then monitored, in fields as diverse as oncology, haematology, cardiology, and neurology.

6

Therapeutic Applications

The ionising effect of radiation can quite naturally be useful in therapy by destroying supernumerary or abnormal cells. When a radionuclide is attached to a substance which aims to concentrate in a certain type of cell, it can destroy these same cells. This is the simplified principle of targeted radiotherapy: the radioactive source attached to a drug or vector plays the role of a toxic load with local effects.

The property of a radiopharmaceutical that causes it to concentrate in a particular tissue or organ – in other words its specificity – is uniquely due to the property of the vector, that is to say the molecule to which the radionuclide is attached. Iodine, in the form of iodide salt, that is used to treat thyroid cancer, is an exception because this element – whatever its saline form may be – spontaneously accumulates in the thyroid tissues whether these are cancerous or not, and therefore does not need to be combined with a vector. The vector's specificity is shown by its tissular radioisotopic distribution. The image obtained from the gamma radiation of a gamma-emitting radionuclide attached to a vector is an exact picture of this molecule's distribution in the patient's tissues (also called biodistribution). Replacing the

gamma-emitting isotope of this diagnosis radiopharmaceutical with a beta- or alpha-emitting isotope will not change the labelled molecule's tissular biodistribution. Contrary to gamma-emitting radionuclides, ionising-type irradiation will affect infiltrated cells in a radically different manner. Hence, this radionuclide substitution leads to the transformation of an imaging radiopharmaceutical into a therapy radiopharmaceutical, with a local cellular destruction effect. In theory, this principle seems to be very simple; in practice, it is only effective if the substitution of one isotope for another on the same vector can be done without any chemical and biological modification of the latter.

The technology can be applied well beyond metabolic mechanisms, and any biologically "active" molecule present is potentially worth labelling – whether one wishes to study hormonal or enzyme mechanisms, the interaction of ligands and receptors, substance transport mechanisms, or even cellular reproduction. It would be worth replacing the frequently used term metabolic radiotherapy by internal radiotherapy, molecular radiotherapy, or more precisely, targeted radiotherapy.

I. METABOLIC RADIOTHERAPY

Radionuclides which intervene in the metabolism of a cell – i.e. in the mechanism of its biological functioning – can be used for therapeutic purposes since their damaging effect will operate within the actual cell itself. This is basic metabolic radiotherapy.

Iodine naturally and specifically accumulates in the thyroid; treating patients with radioactive iodine has proven to be unexpectedly effective in all of these tissue affections. Iodine was the first radionuclide to be administered to man on a large scale with a therapeutic goal in view, and has given no reason to doubt its effectiveness since the 40s. Given orally and in its simple sodium salt form, Iodine-131 is used for treating benign thyroid diseases

such as Grave's disease (diffuse goitres, an immune system disorder which disrupts regulation of the secretion of thyroid hormones), toxic forms of goitres, hyperthyroidism, and in the elimination of benign thyroid nodules or post-surgical residuals. It is also used in therapy for treating malignant conditions (thyroid cancer), including metastases, as long as the tumour is able to accumulate this element. Iodine-131, an emitter of both γ and β^-, is also used at a weaker dose for imaging the thyroid and any of its possible metastases, while the radioisotope Iodine-123 remains limited, in this pathology, to its current use in imaging.

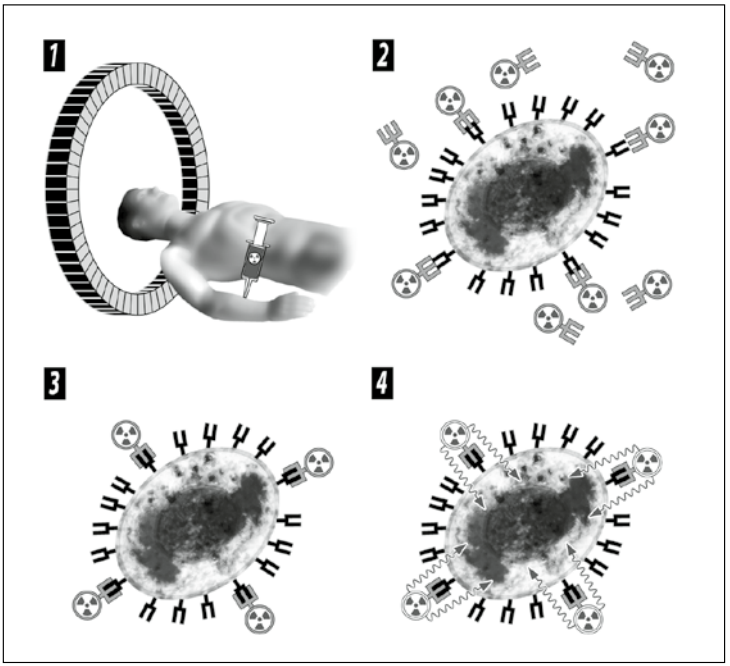

Figure 10 | Metabolic radiotherapy principle: the radioactive substance linked to a vector (drug) is injected to the patient (1). There are large numbers of specific receptors on the surface of the tumour cell, which the vector is able to recognise. The vector binds to the cell receptors (2). As unbound molecules are naturally eliminated from the body (3), the radionuclide slowly disintegrates and destroys any cell present in its immediate surroundings by emitting alpha or beta-minus particles.

Today, radioactive iodine remains the favoured treatment for this type of cancer, and was for a long time the only really effective metabolic radiotherapy tool. There is no other radioisotope-tissue pair displaying such a strong bond and such evident specificity.

Structural analogies between the components of bones and certain radioactive atoms could explain the mechanism underlying the action of substances used in the palliative treatment of pain in patients suffering from bone metastases.

The formation of these metastases – particularly in the evolution of breast or prostate cancers – can be extremely painful, and is today considered as the beginning of the cancer's terminal phase. Treatment becomes extremely radical, and healing – even remission – is very unlikely. High doses of morphine are usually given as a pain killer. Among other methods, products such as Strontium-89, Rhenium-186 and Samarium-153 in the form of salts or complexes have been developed to provide at least partial relief from the intense pain which is generated by the metastases that develop on contact with bone tissue.

It seems that their analogy with bone constituents enables them to insert themselves between the metastasis and the bone tissue, thus significantly reducing pain, and even enabling patients to continue their anti-cancer treatment as outpatients. In some cases, recent observations have shown a reduction, and sometimes a halt, in the disease's evolution. Researchers even think that in view of the specificity of these agents, they may, at higher doses, promote the disease's regression.

These observations led to the development of Radium-223 dichloride, initially a pain palliation agent in the treatment of prostate cancer bone metastases which proved to have an impact on survival. Radium-223 dichloride is no longer considered as a pain palliation agent but as a real therapeutic drug which, despite its limited impact on survival, did show for the first time a real advantage for patients. Proposed today as the only alternative for

late-stage prostate cancer patients, this drug is becoming the first blockbuster of the radiopharmaceutical industry, with yearly sales counted in hundreds of millions of US$. Although not on a par with chemotherapeutics, such a success started triggering interest from conventional pharmaceutical industries, which now look differently at radiotherapeutics.

II. LOCAL RADIOTHERAPY

Local radiotherapy consists of injecting a radioactive substance into a specific delineated natural zone or cavity, with a therapeutic effect that will in consequence be limited to this region.

The treatment of rheumatoid arthritis is one of the few non-oncological pathologies that can benefit from this internal radiotherapy technique.

Rheumatoid arthritis is a phenomenon that is allergic in origin, and which leads to the abnormal proliferation of synovial cells filling the cavity between the two segments and promoting the destruction of the cartilage cells. This auto-immune disease is treated in the first place with anti-inflammatory substances to halt its progression. At a later stage, physicians use drugs often analogous with anticancer treatments (cyclophosphamide, methotrexate, TNF-alpha) to reduce the abnormal growth of synovial and cartilage cells. A treatment possibility is the destruction of supernumerary cells with drugs or through surgery, coupled with a palliative pain treatment (corticosteroids).

The substances used in these therapies often lead to undesirable side effects. Radio synovectomy may be recommended when the doctor finds that traditional therapies have failed, and when the disease becomes more acute and spreads to other joints. This internal radiotherapy technique, known since the late 60s, is based on the destructive effect of β^- radiation. A radionuclide, chosen on the basis of specific physico-chemical and radiological criteria, is injected into

the joint cavity containing the synovial fluid. Along with its half-life, the beta emitter's energy is of utmost importance as it determines the average effective distance. Different radionuclides are used for this purpose: the least energetic Erbium-169 (9.5 days half-life, 3 mm average effective distance in the tissue, with a 10 mm maximum) is prescribed for hand joints; Rhenium-186 (3.7 days half-life, 12 mm average distance, 37 mm maximum) is preferred for wrists, elbows, shoulders, and hips; Yttrium-90 (2.7 days half-life, 36 mm average distance, 110 mm maximum) is used for injection into the knees.

In order to prevent the isotope from spreading outside the interjoint space, it is trapped in neutral microparticles and the product is injected in the form of an aqueous suspension.

The results show a spectacular recovery of the capacity to use these joints, a pain reduction in most cases, with an improvement still clearly marked three years after the first injection without the need for additional treatment. The use of these products is limited by the lack of specialists in this technique, the need for in-patient treatment and, in most countries, the absence of reimbursement.

III. RADIOIMMUNOTHERAPY

The combination of antibodies and radionuclides leads to the formation of highly specific drugs which allow either the imaging or the treatment of certain types of pathology due to their involvement in the natural immune mechanisms. This is the radioimmunodiagnosis technique that can be combined with radioimmunotherapy.

In a process of self-defence against external chemical or biological attacks (antigens), the human body is able to develop specific substances (antibodies) that can destroy these foreign invaders. This is the basis of our immunological system's functioning that produces new antibodies each time new external molecules or foreign cells – which are not recognised as being fully part of the body – enter the cells or the tissues. In fact, antibodies recognise a molecular

sub-structure of these external entities which is called an epitope. Abnormal cells and precursors of cancerous cells are also eliminated through this mechanism. Unfortunately, at a certain stage some of them succeed in colonising a tissue and give way to a tumour. The reason why these abnormal cells are not recognised by our immune system has not been elucidated. From this stage, growing cancer tumours are not considered as foreign entities anymore, and therefore are not destroyed by the immunological system. However, they show some specific epitopes in larger amounts than surrounding normal cells, and as a result they can be recognised by matching antibodies.

Antibodies can be used to fight diseases; as they are specific to an antigen, they are ideal vectors for targeting tissue as long as they are also capable of crossing the biological barriers. Numerous antibodies that selectively target tumour antigens have been developed over the course of the last three decades. They are used in the context of immunotherapy treatments. The pathogen potential of these substances is increased by grafting a β^- or α emitting radiotoxic substance onto them in order to transform them into a radioimmunotherapy product. The use of γ radionuclide emitters in the place of β^- emitters enables the distribution of these antibodies to be displayed, and gives access to radioimmunodiagnosis or immunoscintigraphy tools.

Numerous technical barriers have had to be crossed as these products constitute the pinnacle of complexity of a drug: they are subject to the constraints of pharmaceutical quality manufacturing, to the obligations linked to the use of biological material of animal or human origin, and to compliance with every safety aspect linked to the use of nuclear materials. Polyclonal antibodies (originating from several stem cells) of animal origin have given way to humanised chimeric antibodies (the animal origin part must not be recognised as foreign by the human immunological system), and practice is increasingly moving towards the production of modified monoclonal

antibodies of human origin (single stem cell source). In this way, abnormal generation of human anti-mouse antibody (HAMA) is avoided. The radioactive labelling methods for these molecules do not target a precise site on the antibody, but ensure that the radioisotope is fixed in a part of the macromolecule that does not interfere with the antigen recognition zone. Today, labelling chemistry has advanced to such a degree that, in practice, it is possible to pair almost any type of isotope with any antibody without losing the biological properties of this antibody.

The trial-and-error period looking for the ideal radioisotope seems to be coming to an end, and several radionuclides such as Iodine-131, Yttrium-90, and Lutetium-177 stand out for reasons essentially linked to production ease, to chemistry, safety, and dosimetry issues, and above all to their physical properties – such as half-life and energy. A few other isotopes are still being put forward and studied by researchers, but this is presently limited to Holmium-166 and Rhenium-188. A new set of alpha-emitters are also evaluated in this modality, among which Astatine-211 and Actinium-225.

On this basis, a number of antibodies have already been the subject of evaluation: for example, we can mention antibodies targeting CD20, CD21, CD22, CD37, HER-2, ferritin, or HLA-DR. These macromolecules have principally been labelled with Iodine-131 or Yttrium-90. Labelling with Technetium-99m or Indium-111 has enabled the distribution of certain of these substances in the organism to be studied. New approaches for imaging are considering using Gallium-68 or Zirconium-89. Among radio-labelled antibodies – limited to imaging and which are being developed or marketed – we can mention arcitumomab labelled with Technetium-99m for imaging colorectal cancer, capromab labelled with Indium-111 for imaging prostate cancer, antigranulocyte MAb 250/183 labelled with Technetium-99m for imaging infections and inflammations, and satumomab labelled with Indium-111 used in the immuno-scintig raphy of colorectal and ovarian cancers.

The first two anti-CD20 antibodies, tositumomab and rituximab – labelled respectively with Iodine-131 and Yttrium-90 – were made available on the market in 2002 for the treatment of patients suffering from non-Hodgkin's lymphoma resistant to traditional chemotherapy, including immunotherapy. New approaches for this disease are considering the use of Lutetium-177 as a new and more powerful radionuclide. Clinical studies in progress should demonstrate that these products are even more effective when administered as the first-line treatment.

RADIOIMMUNOTHERAPY AND LYMPHOMAS

Antibodies are substances with very complex structures. They are produced by the organism, and are intended to initiate a reaction in order to destroy a foreign body. Antibodies are capable of recognising a fragment of an infectious agent or a molecule that is foreign to the organism, called an antigen. Each antibody has its specific attachment sites. Our organism is capable of producing new antibodies each time it comes in contact with an undesirable substance. As and when contact with external elements occurs, our organism builds natural barriers that contribute to our internal defence mechanism called the immune system. The different antibodies present in our organism number several million and are permanently on guard. In the context of an external threat, our immune system is capable of producing millions of copies of the antibody specific to this aggressor in order to fight it. Obviously, it can only do so if it has previously been in contact with this aggressor or this disease. An allergic reaction is an excessive reaction on the part of the organism to an external intruder for which the body is usually prepared, that is to say for which the organism has already built its antibody. Vaccination is a form of prevention that works by introducing these elements into the organism prior to any contact with the disease. This very simplified explanation helps us understand that, normally, a disease only occurs

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in the case of a first contact with the infectious agent, or else when the organism is not capable of reproducing its own defence agents quickly enough.

As a tumour is made up of abnormal cells, one might think that the organism would be capable of developing antibodies likely to initiate its destruction. Unfortunately, tumour cells originate from the individual's normal cells, and retain certain characteristics of these healthy cells. As a consequence, they are not recognised as foreign cells by the organism – and are therefore not fought against. On the other hand, some new antigens which do not exist in healthy cells can be identified in the tumour cells. Tumour cells can also bear much larger amounts of specific antigens of a certain type. The exact term is that cells express – or even over-express – these antigens. Biologists have succeeded in developing antibodies that specifically target these antigens and are therefore able to attach themselves mostly to the tumour cells. All that remains is to transform these new vectors into media for a toxic substance capable of destroying the tumour cell. This is the basis of immunotherapy. If this toxic substance is a gamma-emitting radioisotope, a radioimmunodiagnosis or immunoscintigraphic product will have been conceived, and it will serve to show the distribution of the labelled antibodies in the tumour. By using a beta-minus or alpha-emitting radioisotope, the radioimmunotherapy product will serve to destroy this same cell.

The concept seems extremely attractive. A number of technical barriers have had to be crossed. The initial "artificial" antibodies were formed from tissue taken from mice or rats. They had the disadvantage of being, in part, rejected by the human organism which began making anti-mouse antibodies. In a second approach, biologists succeeded in creating mixed mouse-human antibodies called chimeric antibodies, and they have only recently been able to easily construct human antibodies.

In between, radiochemists also developed methods to label these molecules with different radionuclides. As these molecules are extremely large, wanting to develop a method targeting a precise function of the

molecule was pointless. Rather, chemists made sure they could attach a radionuclide to a part of the macromolecule that does not interfere with the zone that serves for recognition of the antigen. This chemistry is now fully developed and mature, and it is possible to pair (almost) any type of isotope – including alpha isotopes – with (almost) any antibody.
The application of these principles is described in the "Non-Hodgkin's Lymphoma" example below.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma is a disease expressed by the formation of tumours in the lymphatic system. More than 60 distinct lymphoma sub-types have been identified. The difference with Hodgkin's disease is only visible when the cells are analysed under a microscope. Hodgkin's disease is characterised by the presence of a very specific type of cell called the Reed-Sternberg cell.
Generally speaking, the painless swelling of a lymph node marks the first signs of the disease. Lymph nodes being situated in all parts of the body, the first discomfort depends on the location of this abnormal cell development. In the case of the digestive system, the initial consequences are expressed by nausea, vomiting, or abdominal pain, while a node in the stomach may affect the breathing capacity. Headaches – sometimes combined with visual problems – can indicate a brain tumour, and when the bone marrow is affected, anaemia will be the first consequence. The disease may cause a hyperactive immune response. As the symptoms are often exacerbated when the body is fighting an external threat such as an infection, this response is expressed by fever, tiredness, and weight loss. The immune mechanism behind this phenomenon is similar to that causing itching for example. It is considered to be a fatal disease, however more than half of sufferers have a survival expectancy of more than 5 years – and this period is regularly increasing.
The disease affects all age groups, but half the cases are people aged 60 or more. There has clearly been an increase of this disease over the

last 20 years, for which there is no explanation; neither can its origin be explained. It became known to the general public via famous cases like those of Jacqueline Kennedy Onassis and Shah Mohammed Reza Pahlevi.

Treating Non-Hodgkin's Lymphoma

Major efforts have been devoted to the development of a treatment for non-Hodgkin's lymphoma, due to the limited response rate to current treatments and the high rate of side effects associated with chemotherapy and external radiotherapy methods. Although the development of these methods over the last 40 years has extended the remission time of the disease, it hasn't yet shown any significant improvement in the survival rate.

From Indium to Yttrium to Lutetium

Several monoclonal antibodies have been developed and marketed that are of animal or chimeric origin – that is to say mixed, and therefore formed of molecules coming from both humans and mice, and directed against the CD20 antigen present on the surface of malignant lymphocytic B-cells typical of the disease to be treated. These antibodies have a therapeutic activity by themselves, as they block the functioning of these malignant cells by preventing them from reproducing. Unfortunately, due to their mechanism, they cannot claim to completely destroy these cancerous cells, and the treatment – though effective – only manages to slow down the evolution of the disease.

Knowing that these antibodies target the cells to be destroyed, it becomes obvious that by combining them with a toxic substance an effect on this target could be expected, directly on the tumour cells and within the immediate environment.

In order to verify whether the antibody is actually distributed to these malignant cells and to them only, a radioactive atom is grafted onto one of these antibodies – specifically, Technetium-99m, Iodine-123 or Indium-111. Labelling is obviously carried out in such a way so as not to disturb the interaction between the antibody and the antigen targeted. The two radioisotopes are gamma emitters, and the images obtained

after injecting the labelled products helps confirm the initial hypothesis. At the same time, these new labelled molecules become specific imaging agents for the disease. should one want to use PET imaging instead of SPECT, then these antibodies could be labelled with Gallium-68 or Zirconium-89.

Although Iodine-123 and Indium-111 are both Auger electron emitters which could be used in therapy, the concentration on the surface of the B cells is too weak to be effective in any way. It was therefore preferable to replace these two isotopes with Iodine-131 or Yttrium-90 respectively, both high-energy beta emitters. New therapy radiopharmaceuticals were born. The two substances provide convincing results, each with their own advantages and drawbacks. Thanks to this work, the yttrium and iodine labelled substances were brought on the US market in 2002 and have been available in Europe since 2004. Taking into account the lack of perspective as regards this type of therapy, miracles must not yet be expected. It is preferable to take small steps forward and demonstrate gradual improvements in patients. Thus, these molecules have only been authorised for certain categories of patients suffering from a non-Hodgkin's type of lymphoma, and at a very precise dose of radionuclide. In particular, treatment is only administered to people for whom previous chemotherapy has failed – including immunotherapy using the same antibody.

Despite such limitation, these products have given positive results, demonstrating their therapeutic value as compared with existing therapies, one of the first new victories for nuclear medicine.

Studies are in progress, firstly to demonstrate that the treatment is at least as effective – if not more – when given at an earlier stage, and secondly to increase the dose in order to obtain an even greater response rate. These studies, which need to take place on a wide scale, will still require several years of work before authorisation is given for an extension to the indication. Nevertheless, these examples show the significance and the effectiveness of this method. A number of radiolabelled antibodies are being evaluated with a view to treating various forms of cancer, and could be marketed within the next five years.

IV. TARGETED RADIOTHERAPY

Targeted radiotherapy combines a therapeutic radionuclide, mainly a β^- emitter, with a smaller organic molecule serving as the vector and which will target the tumour cell.

In order to get round the biological stability of antibodies and the difficulty of producing them, some teams have started to label smaller-sized molecules. After trials with immunoglobulin fragments, biologists and chemists developed an interest in synthetic peptides. In fact, all biologically active molecules recognised by a receptor can serve as a vector. On the other hand, the specificity for a given target becomes of first importance, and the idea of working with antibodies started from the principle that the larger the molecule, the greater the chance of it being recognised by a single type of cell only. This theory is no longer put forward since it has been possible to show that a limited number of recognition sites participate in the antigen-antibody interaction, and that in this case the antibody can be reduced to a very small structure which can be reconstructed by combining amino acids in an appropriate fashion. This is called antibody engineering. Even smaller combinations of amino acids (peptides) can do the job. Those are not targeting epitopes anymore but interfering with the biology of the cell in particular, with certain specific receptors expressed on the surface of tumour cells. This particular chemistry opens a new avenue for radio-labelled molecules, and peptides form another vector class from which a great deal is expected.

In the peptide class, certain products are a few lengths ahead. Somatostatin analogues (i.e. octreotide, pentreotide, lantreotide, and depreotide which are labelled with Iodine-123, Technetium-99m, or Indium-111) provide specific images of various cancers' tumours and metastases due to their particular affinity for over-expressed receptors in these cells. The substitution of these imaging radionuclides with therapeutic radionuclides (Rhenium-188, Yttrium-90, Iodine-131, and now Lutetium-177 as a priority) allows the use of these same molecules to be considered in the treatment of patients. The first

molecule of this new family has completed phase III clinical trial and is close to obtaining a marketing authorization (2017). Several analogues are now under development and could reach the market for analogue indications within the next five years. All of these new molecules are labelled with Lutetium-177.

Peptides have also been explored in the prostate cancer indication, and surprisingly good survival results have been shown in late-stage metastasised patients with Lutetium-177 labelled molecules.

V. ALPHATHERAPY AND ALPHA-IMMUNOTHERAPY

Alpha emitters have a powerful destructive capacity, due to the large size of the ejected particle and as a consequence to its much higher ionization potential compared to beta emitters. This size also limits the zone of interaction with neighbouring cells. Several tenths of a millimetre of matter are sufficient to stop this radiation. Therefore, an alpha particle has the ideal profile for use in cancerous cell destruction at a short distance. Combined with the techniques referred to previously, one can speak of alphatherapy and alpha-immunotherapy.

Unfortunately, detecting alpha radiation is much more difficult than detecting beta or gamma emitters, and becomes impossible once the substance has been absorbed or ingested. As a consequence, accidental contamination will also be more difficult to localise and this limitation will greatly influence its production, transport, and implementation in the medical world.

Also, due to their aggressive nature with regard to all cells whether healthy or sick, alpha emitters can only really be applied to patients using extremely selective vectors which are rapidly eliminated from the body when they do not bond with their target. In this case, the effects of alpha emitters concentrate in the circulatory system (veins, arteries) and the organs involved in metabolic functions (liver, kidneys, bladder). This is unlike beta emitters which, due

to their greater energy, destroy almost as many cells, but from a greater distance and therefore in a more dilute way inside the body. The notion of an effective half-life – which gives information about the time period during which the isotope retains its destructive character in the targeted organ and which is connected to both the isotopes' half-life and the biological half-life – takes on renewed importance.

Finally, alpha emitters also suffer from greater negative publicity when compared to other radioisotopes because their only applications known to the general public are essentially military.

However, if the specificity of vectors could really be improved, alpha emitters would be ideal isotopes for use in anti-cancer therapy.

The isotopes used in metabolic therapy have very short half-lives, and even extremely short compared with the better known alpha emitters like uranium or plutonium. In fact, only three isotopes have so far demonstrated their use and potential for application in research laboratories: Actinium-225 (half-life of 10.0 days) which has the particular characteristic of producing four alpha particles during its decay, Bismuth-213 (half-life of 45 minutes), and Astatine-211 (half-life of 7.2 hours).

As surprising as it may seem, alpha radiation was the first to be applied in nuclear medicine, on the basis of natural radioelements. Radium salts were also used for therapy. The first alpha emitter that was injected as an approved drug was Radium-224 Dichloride (half-life of 3.62 days), used in the treatment of ankylosing spondylarthritis (Bechterev's disease). This product was only available in a limited number of countries such as Germany, and was discontinued due to toxic side-effects. Additional exploration of this area led to the first commercial application of Radium-223 Dichloride in prostate cancer treatment, which must now be considered as a commercial success. Researchers are continuing to explore this avenue, trying to get round the above-described constraints.

Grafting an alpha-emitting radioisotope onto a vector directed against a biological target was first attempted twenty years ago with Bismuth-213. Tests on man with anti-CD33 type antibodies or labelled tenascin have been explored. Definite effectiveness has been noted, but research is progressing slowly as it follows results from a successive increase in applied doses. The maximum dose tolerated – i.e. before side effects appear – has not yet been reached, indicating that further improvements in the state of health of patients are to be expected. Initial envisaged indications were related to gliomas (brain cancer) and lymphomas.

Actinium-225 trapped in a molecular cage, itself attached to an antibody or peptide, will play the same role as the above-described beta emitters. Nevertheless, its fire power is four times as great since it can release four alpha particles one after the other. The researchers who developed this technology named it the "nanogenerator": a form which, once located on its target, is capable of generating several radioactive particles at a molecular scale. *In vitro,* these molecules have already demonstrated their effectiveness against various human cancer cells (leukaemia, lymphoma, breast, ovaries, and prostate). Initial clinical trials have been performed in patients with a glioma (brain cancer), non-Hodgkin's lymphoma, and acute myelogenous leukaemia.

In France, the town of Nantes has access to a unique tool: a 70 MeV cyclotron capable of producing very complex radionuclides in industrial amounts. It has been operational since 2009, and is also used for research and development. This tool is twice as powerful as the largest Europe-based cyclotron dedicated to nuclear medicine, and also allows alpha radionuclide emitters to be produced in much greater quantities.

The most recent developments in Alphatherapy are based on the extension of successful beta-labelled radiotherapeutics. In particular, almost all companies that have developed a Lutetium-177 labelled drug are now considering replacing the lutetium with an

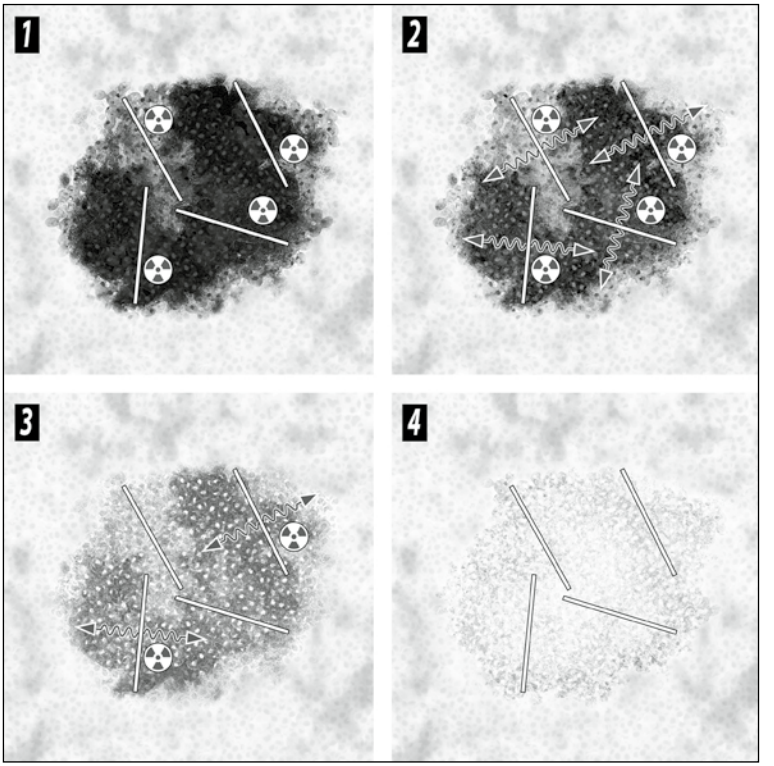

Figure 11 | Brachytherapy: solid radioactive units (seeds, wires...) represented here in the shape of long rods are implanted in the tumour mass. Radioactivity then slowly destroys the surrounding (i.e. tumour) cells. The metallic implants will either definitely remain on site (prostate) or be removed later, depending on their size.

alpha-emitter such as Astatine-211. While Lutetium-177 with its beta emission and high energy is intended to destroy larger tumours but only has a limited effect on very small tumours, Astatine-211 would be greatly efficient in micro-metastases – and even isolated or individual circulating tumour cells. A consecutive beta then alpha treatment would be equivalent to a broad treatment followed by a deeper cleaning of the residual disease and a tremendous increase in efficacy, with the aim to totally destroy every tumour cell.

BRACHYTHERAPY AND PROSTATE CANCER

Brachytherapy (from the Greek *brakhus*, meaning short, in other words therapy at a short distance), is a modality used in the field of radiotherapy based on the direct contact between the solid irradiating source and the organ to be treated. Some experts prefer to use the term "curietherapy". In practice, it consists in implanting an irradiating source in the tumour to be destroyed, or in a cavity, for a predetermined period of time. Initially, brachytherapy was limited to the treatment of cervix cancers. This remains the most frequent application in many developing countries with no access to more efficient therapies. These radioactive implants – initially labelled with radium, and now with iridium, caesium, strontium, or iodine – can take on any desired form. In the case of breast cancer, curved wires are used which remain in contact with the tumour in the breast for several hours or days. Brain tumours can be treated, in addition to surgery, using radioactive balls which are temporarily placed in this new cavity.

However, all these applications remain very limited because they are difficult to implement (they require special environment and equipment), are little-known, and are non-specific (results depend on the operator's experience). Meanwhile, brachytherapy has found its niche in the treatment of prostate cancers. Prostate cancers develop very slowly, and affect a large part of the male population over the age of 75. Taking the concerned age group into consideration, mortality linked to other pathologies still remains predominant. It would seem that more than 80% of men who live beyond the age of 80 have the disease without being affected by it, and without even being conscious of the fact. Unfortunately, this disease also affects men under 50 who hope to be able to find a non-traumatic way of healing. As with all other cancers, the chances of healing are so much the greater when the disease is detected early on. It is nevertheless estimated that this disease takes almost 15 years to develop metastases, allowing patients and physicians some time to choose and intervene.

As with breast cancer, surgery remains the most common solution in prostate cancer. It nevertheless does have a number of disadvantages, some of which are annoying, such as urine retention deficiency and sexual impotence. For surgery to remain effective, it is necessary to remove the entire tumour contained in the prostate – and therefore several millimetres of healthy tissue as well. Surgeons often have to cut into muscle tissue used in urinary or erectile functions. This loss of functional capacity is no longer considered to be insignificant for people who are otherwise well despite their age – and it is even harder to accept for younger patients.

Brachytherapy comes to the aid of these patients by offering an alternative to surgery in the form of radioactive metal implants which are placed and confined within the tumour. About a hundred of these small pieces, less than a millimetre long (seeds), are implanted directly into the tumour tissue under local anaesthetic. Their distribution in the tumour is arranged very precisely in order to obtain uniform radiation of the cancerous tissues by the Iodine-125 or Palladium-103 which they contain.

Several tens of thousands of patients have already benefited from this technology, which has become routine in the United States over the last 20 years. The emphasis is placed on its advantages in everyday life: a very short stay in hospital and the absence of side effects. The metal implants – which lose their radioactivity after a few months – remain in place for life. They do not cause any problems, unless the patient dies in the weeks following the operation as cremation is rendered impossible by the fact that the radionuclide could be released into the atmosphere. For this unique reason, the acceptance of this technology was limited in Japan.

It must however be mentioned that this technique requires extensive technical support, and the operation can only be carried out by a trained and competent team. The urologist or oncologist who first discovered the cancer may recommend this procedure. It is obviously carried out in the presence of an anaesthetist, but it also calls for a nuclear physician

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or a radiotherapist who is, depending on the country, the only one authorised to handle radioactive sources. Furthermore, as placing the seeds can only be correctly carried out by displaying them with an ultrasound device, the presence of a specialist in this technology is essential. Finally, special equipment which requires a suitably large budget is essential, and for the moment this is taken care of by the manufacturer supplying the implants.

VI. THE THERANOSTIC APPROACH

The efficacy of a radiotherapeutic agent is directly linked to the specificity of the drug distribution in the cells to be destroyed. This biodistribution is highlighted with the analogue radiodiagnostic agent which will show the physician where the therapeutic molecule will accumulate and affect the cells or tissues. The higher the concentration in the tumour cells, the more efficient the radiolabelled drug – that will be based on the same molecular structure. On the contrary, the absence of a specific signal or the lack of radiodiagnostic accumulation in already identified tumour tissue indicates that the treatment will be of no efficacy, and should therefore be avoided. Hence, a lack of positive imaging or an unexpected accumulation in healthy tissue can also lead to the conclusion not to start a treatment in those patients, as they will be non-responders or be affected by serious side-effects. This pair of analogue radiodiagnostics/radiotherapeutics is called a theranostic pair. This diagnostic tool is intended to identify positive responders to the subsequent treatment, and almost ensure the success of the therapy.

The theranostic concept can be extended to the combined "imaging agent" and "non-radioactive therapy" (e.g. chemotherapy), provided it has been proven that the therapeutic agent accumulates and affects exactly the same cells as the ones identified by the diagnostic imaging agent. This concept is now explored to a much

larger extent, and will definitely impact the cost of health by reducing the number of expensive treatments that have no efficacy on patients anyway.

VII. RADIOTHERAPEUTIC SUBSTANCES

In summary, the following table gives a non-exhaustive list of products labelled with a β^- radionuclide emitter or an alpha-emitter, used in internal radiotherapy and available on the European market. Other yet more specific products are available in the United States, within the scope of very precise indications. Products with larger markets and intended for a wider group of patients are just beginning to emerge, and are described in more detail in the preceding paragraphs.

Isotope	Chemical form of the radiopharmaceutical	Indications
Erbium-169	Colloidal citrate	Radiosynovectomy
Iodine-131	Sodium iodide	Thyroid diseases diagnosis and therapy Labelling of molecules for therapy
	lobenguane (MIBG)	Oncology therapy (pheochromocytomes, neuroblastomes, thyroid medullar carcinomas)
	Esters of saturated acid	Hepatocarcinomas
Lutetium-177	*Diverse peptides and antibodies linked to this radionuclide under late-stage development and expected to be marketed between 2017 and 2020*	Neuroendocrine tumours therapy Prostate cancer therapy Non Hodgkin lymphoma therapy

Phosphorus-32	Sodium phosphate	Palliative treatment of proliferative polycythaemia and thrombocythaemia Treatment of myelocyte chronic lymphocyte leukaemia
Radium-223	Radium Dichloride	Palliative treatment of pain linked to bone metastases and treatment of metastasised prostate cancer
Rhenium-186	Etidronate	Palliative treatment of pain linked to bone metastases
	Colloidal sulphide	Radiosynovectomy
Samarium-153	Lexidronam	Palliative treatment of pain linked to bone metastases
Strontium-89	Chloride	Palliative treatment of pain linked to bone metastases
Yttrium-90	Colloidal citrate	Radiosynovectomy
	Chloride or nitrate	Labelling of molecules for therapy in oncology
	Ibritumomab tiuxetan	Non-Hodgkin lymphoma therapy

VIII. THE DOSE ISSUE

Therapeutic radiation is of a different type than that used in diagnosis, and the doses administered are often much higher. Is there a dose above which the risk to the patient becomes higher than the benefit gained in a therapy context? There is no obvious answer.

When a treatment shows a certain level of effectiveness at a given dose, increasing that dose may lead to an improvement in the treatment and to faster healing. For a pharmaceutical product, the feasibility is often almost immediate because in most cases the threshold beyond which the first symptoms of toxicity may appear is tens, if not hundreds of times, the normal therapeutic dose.

In the case of radiopharmaceuticals, given the very low quantity of injected product, the toxicity of the vector plays no role. Therapists

find themselves confronted with the problem of radiotoxicity alone, which is well established for a given isotope. The purpose of irradiation is to destroy malignant cells without affecting healthy cells, in the hope that the isotope remains bonded to the vector at least as long as there is an emission of radiation. Therefore, it is the vector itself that should play the main role, allowing a concentration of the radioactivity – and thus limiting toxicity – onto the target cells. Unfortunately, this ideal scenario does not exist. The radiopharmaceutical is first of all injected, it circulates in the veins, and passes through the liver before reaching its target. Molecules that have not been trapped during this stage re-circulate several times through the blood system, before finally concentrating in the bladder after having been eliminated by the kidneys. This process can last from several minutes to several hours, and during this time the isotope irradiates tissues other than those belonging to the initially targeted tumour cell. Increasing the dose also raises the risk of destroying part of these surrounding tissues, and in particular the liver and the kidneys cells are most affected. The time of residence in these organs must be limited to the minimum.

Clinical studies are in progress to increase the dose by a factor of 10, even 30, in the case of certain radiopharmaceuticals that have already had their effectiveness confirmed in clinical trials at low doses. It is possible in some cases to protect the kidneys by adding substances that act on their function (lysine), but at the price of a new type of toxicity due to these additives. However, following initial testing it seems that this treatment is partially effective. The studies are carried out with end-of-life patients whose life expectancy is limited to only a few weeks. Depending on the protocols used, a very clear improvement in the patients' state of health has been noted, and in some cases a remission of several months has even been recorded. We are only at the beginning of these studies, and this phase must be considered as a trial-and-error period spurred by the initial successes. On the other hand, the use of high doses

creates other logistical problems – but these are of less importance compared with the survival of a patient.

Radioactivity is also known for its cancer-generating potential. This point is not to be hidden, but it is estimated that the chances of developing a secondary cancer following treatment with radioactivity (including with external radiotherapy) remain below 5% after 20 years. This is still pretty high, but one should not forget that patients saved by radiotherapy or radiotherapeutics had an initial chance of survival far below these twenty years. On top of this, unlucky patients who develop a secondary cancer at a later stage may probably be cured for this new cancer with a radiotherapeutic agent. One should not forget that patients who developed thyroid cancers as a consequence of exposure to radioactive iodine are cured by treatment with radioactive iodine.

IX. MECHANISM OF ACTION – THE BYSTANDER EFFECT

An irradiated cell is affected in different ways, depending on the type of radiation and the energy released. An electron (beta radiation) will tend to create a negative electrical charge, which will move from one molecule to the other until it causes a rupture of the covalent bond, thus generating an unstable radical form. This free radical will cause a modification of the DNA chain, resulting in the cell's partial inability to reproduce unless quickly repaired by the biological environment. Several simultaneous DNA breaks will lead to a definitive non-reparable destruction of the cell. Due to the electron's small size, this entity can travel a great distance – depending on its energy – before reaching a target and therefore generating a remote disturbance.

The alpha particle – made up of two neutrons and two protons, and several thousand times heavier than an electron – will encounter matter sooner and will have no difficulty in destroying DNA and cells. In most cases, the particle inserts itself into a bond between two

atoms and generates a new – often unstable – entity. If the nucleus is affected, and more specifically its DNA, directly or indirectly, the cell will no longer be able to reproduce and will die.

Several teams of researchers have studied the consequences of bombarding a series of cells with alpha particles while precisely measuring the numbers of particles and cells. They showed that after irradiating 10% of these cells, all of them show a chromosome-11 mutation which is identical to that obtained through direct bombardment. Therefore, irradiating one cell affects all its neighbours. In addition, certain proteins which demonstrate a protective function against malignant changes were produced in greater quantities. Cells communicate with each other, and the death signal emitted by a single cell can be transmitted to other neighbouring cells, leading to their death as well: this is called the bystander effect.

This mechanism has not yet been elucidated, but it offers a definite advantage and partly explains why malignant cells continue to break down even in the absence of radioactivity, long after the end of the radioactivity influence. The doses of radiation required to destroy a tumour are not necessarily equivalent or proportional to the aforementioned tumour's size; actually, a large part of it may disappear once the destruction mechanism has been triggered, simply due to the proximity effect.

Another hypothesis that may explain the effectiveness of radiation in tumour cells is based on their breakdown. Ionising radiation triggers a cell destruction mechanism and the formation of fragments recognised as exogenous (foreign) by the organism. These molecular fragments induce the formation of an immune response and the production of antibodies. It is possible that these antibodies may also recognise these same epitopes on the living cells, and thus participate in their elimination. This hypothesis could explain why certain patients show signs of continued healing even a long time after treatment has ended. It could also help understand why others spontaneously healed.

X. THE LIMITATIONS

Officially, metabolic radiotherapy products are only developed to be administered to adults between the ages of 18 and 65. Specific studies are necessary to include elderly people and patients suffering from other equally incapacitating diseases such as diabetes, liver or kidney failure, or patients with severe heart problems. Children are not supposed to benefit from this technology. Finally, this technique will not be used with women who are pregnant or breastfeeding.

In practice, things are quite different. On the one hand, most people suffering from cancer are older than 60 and have developed other health complications. On the other hand, this therapy is often suggested as a last resort after other procedures have failed. Physicians are sufficiently responsible, and know better than to take the risk of administering these products to patients at the limit of the therapy scope.

If the side effects of radiotherapy might interfere with those of a parallel, pre-existing illness, the decision is more difficult. The undesirable effects linked to liver, renal, or heart failure may prove to be more dangerous for patients than the radiotherapy treatment. Many biological parameters as well as possible interactions with other drugs used in common treatments must be taken into consideration. In most cases, death occurs as a consequence of a general organism weakness, itself induced by one of these treatments.

So far, we have limited our descriptions to the development and use of radioisotopes in relation to the patient. Nevertheless, patients will only be in contact with radioactivity once or twice during the course of the treatment. Medical staff, on the other hand, are in permanent contact with several patients undergoing treatment, and are therefore subject to this radiation on a daily basis. Protective equipment is of course implemented in each hospital. Nurses and physicians are also equipped with dosimeters and are monitored regularly, as with any activity linked to radioactive material. The rules of protection described elsewhere obviously apply to medical staff as well. They can be summarised in three words: time, distance,

and protection, and detailed as follows: reducing the time spent in a radioactive environment as much as possible, and therefore the time spent with patients being treated; increasing to the maximum the distance separating them from the radioactive emitter, and therefore from the patients; and finally, taking maximum advantage of the means of protection provided, such as partitioning, windows and lead-lined equipment.

Very strict rules are put in place for the release of a patient who has been treated, and have more to do with their waste products' radioactivity level (urine, faeces, perspiration) than with their own body radioactivity. In all cases, the risk to the family environment will always be less than that run by medical staff. Some countries like the United States prefer to minimise the irradiation risk to their staff by releasing patients sooner, considering that contamination linked to waste products is of lesser importance. The two concepts are debatable.

These considerations put the emphasis on other limiting criteria such as the access to care through the number of equipped rooms and the availability of competent staff, whether they are doctors or nurses. This technology will not be able to develop unless the infrastructure necessary for its setting up meets the demand.

SUMMARY

A radioactive substance that targets a specific tissue will provide a usable image of this area if the radionuclide used is a gamma or beta-plus emitter, or will partially destroy this area if it is a beta-minus or alpha emitter. In theory, any substance capable of giving a specific image of a tumour can be converted into a therapy product if the diagnosis radionuclide is replaced by a therapy radionuclide.

Things are not that simple in practice because the ideal therapy radionuclide – the one that will only destroy the cancerous cells – does not exist, and account must therefore be taken of all its physical and chemical properties.

Iodine-131 has become the reference treatment for thyroid cancers due to its specificity to thyroid cells, whether cancerous or not.

More complex mechanisms help to explain the effectiveness of Strontium-89, Rhenium-186, and Samarium-153 in the palliative treatment of pain from bone metastases. Radium-223 has shown a positive effect on the survival in these same patients, and is becoming the first blockbuster in the radiopharmaceutical industry. The most recent research results have shown a preference for Lutetium-177 as a beta emitter, and most of the new drugs that will reach the market are based on this radionuclide.

Injected locally, Erbium-169, Rhenium-186 and Yttrium-90 are used in the treatment of rheumatoid arthritis. This method is called **radio-synovectomy.**

Radioimmunotherapy aims to destroy cancerous cells produced as a result of an immune system dysfunction, targeting the antigens of abnormal cells in particular.

In theory, most receptors located on malignant cells can be targeted by vectors onto which a radionuclide has been grafted. In practice, several tens of these new labelled molecules – in particular peptides – have been successfully tested with different types of cancer, and will reach the market very soon.

Alpha emitters present an even greater therapeutic potential, but their use still requires further development.

The combination of radiodiagnostics followed by the use of analogue radiotherapeutics opens the way for the development of **theranostics**, which aim at selecting and treating positive responders to these therapies.

The mechanisms explaining the effectiveness of radiotherapeutic substances are not as simple as it would first seem. Apparently, cell repair continues to operate well after the radioactivity has disappeared, and not necessarily in proportion to the dose administered (bystander effect, dose effect).

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The Development of Radiopharmaceuticals

Metabolic or targeted radiotherapy applied to oncology has led to some very convincing and promising results. Yet, the successful initial application of iodine in the treatment of thyroid cancer was followed by a long, and apparently unfruitful, period at the therapeutic level. However, these years enabled the mechanisms involved in the action of radioisotopes to be better understood. They also helped evaluate which isotopes were best suited to therapy, improve imaging techniques, develop labelling methods and, above all, find the appropriate means to produce the complex molecules that could serve as vectors. The tools and technology are now available to researchers; meanwhile the industry has become fully mature. Once again, time must be allowed to develop ideal molecules. The first effective second generation molecules only really appeared at the start of the twenty-first century. A number of additional radiopharmaceutical products –the third generation – are under evaluation, and other avenues are being explored in research laboratories, in particular with alphatherapy. The development of a drug requires a great deal of time and money.

The radiopharmaceutical aspect brings an additional constraint, which can however present original and particular advantages in certain circumstances.

This chapter describes the different stages, in sequence, of a drug's development – and more particularly a radiopharmaceutical product, starting from the chemists' discovery of the very first molecular entity to the authorisation of the product's marketing, including the verification stages of its biological, pharmacological and toxicological properties, animal testing, then human testing, and finally the preparation of the final administrative dossier.

WHICH MARKET?

Depending on the therapeutic indications, a new molecule arriving on the market will have cost between 200 and 900 million euros and will have taken from 9 to 12 years of work. Figures can fluctuate greatly depending on the indication, and whether failures are integrated or not. A number of companies are now claiming that some development can require more than a billion Euro. In order to be profitable, a new drug must generate a turnover of the same amount on average within each year following its marketing. Taking the financial stakes into account, choosing the right market is mandatory before researchers commit themselves.

Each company has a strategic marketing unit which evaluates the most promising fields by looking into the future, in order to estimate the real medical needs at the time of launch – so 9 to 12 years from the initial investment decision. Companies carry out market researches to assess the potential development of these future drugs. Requirements in the pharmaceutical field are also linked to the sudden appearance of new pathologies (aids, hepatitis), to behavioural changes (excessive tobacco and alcohol intake, leading to an increase in the number of cancers), and to bad eating habits (leading to obesity). An increase in certain risks (a higher number of diabetics), or the ageing of the population

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(Alzheimer's and Parkinson's diseases) also play an important part in these estimations. In addition, these markets depend on changes in legislation, regulations, and policies (care and reimbursement level for the drug). The value of the market is significant because the cost of developing a product will be practically the same whatever the chosen indication may be. Therefore, pharmaceutical companies fight over profitable niches such as neurology and cardiology, while at the same time neglecting diseases that affect a large number of people (malaria, tuberculosis) but which occur in countries with little or no financial capacity. The pharmaceutical industry has no philanthropic vocation and is obliged to perform financially in the same way as any other profit centres (such as food or automobile industries).

Even if the niche is profitable, the marketing strategy must be capable of forecasting the market share that will be taken by the company in the field in question, without being aware of the progress achieved meanwhile by the competition. The pharmaceutical industry is without doubt in the most competitive market, with the added constraint of a very imprecise economic forecasting. The bet is always very risky. Nevertheless, choices are made and objectives are set on this basis for researchers.

The decision to develop a new radiopharmaceutical product must in principle follow the same rules. Nevertheless, potential markets and production constraints have so far limited profits to rarely more than a tenth of the figures mentioned above. Recent successes have shown that radiotherapeutics are as profitable as chemotherapeutics, with a potentially equal or superior efficacy, and conventional pharmaceutical industries have only very recently become interested in this field. On the contrary, diagnosis will remain the poor parent of nuclear medicine, and will never yield as much income as therapeutics even if more patients are involved. Consequently, the development of diagnostic products can only be profitable if development costs, or else competitive risks, are reduced proportionally. Certain specific parameters show that these developments remain possible still.

I. THE MOLECULE DISCOVERY PHASE

A researcher in charge of "developing a new drug for a defined treatment" quite simply starts with copying: copying nature, and copying the competition. Then, he transforms with a view to improve, of course, and also to meet the pharmacologists' wishes.

Chemists alter molecular forms and structures on the basis of their scientific knowledge and experience, but also their intuition. Each new molecule is tested by biologists. As results progress, chemists try to improve the product's properties in order to obtain a family of new compounds with a certain level of effectiveness. The new molecule set must be able to be patented, therefore it must be original.

This first stage of a vector's development is in fact independent of a radiopharmaceutical's: there are so many molecules available on the market today that wanting to develop one's own vectors is pointless. At the very most, the chemist will be able to modify the structure of the molecule in order to improve a particular property. On the other hand, he will need to find a means of incorporating or grafting a radioisotope onto it without affecting its biological properties.

Recent estimates show that, on average, only one molecule becomes a drug out of 4,000 to 5,000, and synthesising as many requires the lifetimes of several chemists. As radiochemists only use these marketed molecules as a starting point, their chances of transforming them into radiopharmaceuticals are that much greater, and therefore the time period for the "discovery" of a radiopharmaceutical is reduced by just as much.

II. PHARMACOLOGICAL AND PREDINICAL STUDIES

While chemists are kept busy with their reactors, pharmacologists strive to develop a test *in vitro* which will enable them to confirm whether the new molecules are more or less active as compared with the natural substance, or the competitor's molecule, of reference. A

traditional molecule will go through a series of quick and not very stringent tests, allowing the best to be selected (screening). These tests are essentially carried out using living cell extracts such as receptors or enzymes. The ability of a molecule to attach itself to a cell (to bind) or to block or activate an enzyme will also be measured.

A slightly more sophisticated, more extensive, and therefore costlier test eliminates yet more molecules among the tens of interesting ones. The information obtained at this stage simply confirms that the molecules from this initial series interact in the mechanism that enables the pathology to be described, but it doesn't specify whether that interaction helps healing or, on the contrary, makes the disease worse. A partial answer to this question can be obtained by testing the molecules' activity on an isolated organ, like a heart for a future cardiology product, or part of an intestine for a drug being developed for gastroenterology or immunology purposes. At this stage, the biochemist's imagination comes into play. Products intended for neurology, for example, are not necessarily developed using brain extracts.

The third and last stage involves a few dozens of molecules. It is the most thorough because it makes use of preconditioned animals, simulating the indication being targeted.

In oncology, the most usual method consists of treating mice which carry tumour transplants of human origin. These stages are extremely costly, both in terms of money and time.

During the radiopharmaceuticals development phase, a large number of these steps can be reduced. The reason is quite simple: the radioisotope grafted onto the molecule plays its role as a tracer, and imaging allows the molecule to be located immediately. The best substances are selected on the basis of those that show the greatest aptitude to concentrate on the specific tumour, or on any other organ or tissue being targeted. This imaging advantage has already greatly contributed to reducing the number of animals used in pharmaceutical development tests.

III. PHARMACOKINETICS

Pharmacokinetics studies define the time during which the drug is going to reside in the cells, and more generally in the organism; metabolic studies identify the transformation processes, and also the elimination of the molecule.

Absorption, distribution, metabolism, and elimination are four terms that define the drug's evolution once swallowed or injected. Studying these parameters provides information on the speed at which the product is distributed in, then eliminated from, the body (pharmacokinetics), and also on the mechanisms of this distribution (pharmacodynamics). These values help determine whether the product should preferably be given orally or intravenously. Depending on these conclusions, it is the galenist's responsibility to find a suitable formulation. These formulation specialists must take into consideration the body's entrance of the drug (mouth, nose, skin, vein), the speed at which it must distribute in the body, and the final target in which the drug needs to concentrate. A whole range of media enable to accelerate or delay the dissolution time and decide whether the capsule should disintegrate in the stomach or in the intestines. In addition, they indicate when a patch is more suitable than an injection, while confirming that these combinations do not degrade the quality of the product over the course of time. The formulation of a drug goes back and forth an incredible number of times between the galenist and the pharmacokinetic scientist, in order to optimise both the distribution of the medication in the body and the end product's longevity on the pharmacist's shelves.

In the case of radiopharmaceutical products, following the distribution of a labelled molecule in an animal is just as easy as following its evolution after ingestion or injection. As far as the formulation is concerned, radiopharmaceuticals are essentially administered in the form of intravenous injections, using a syringe, and more rarely orally (iodine for thyroid cancer therapy).

IV. TOXICOLOGICAL ANALYSIS

A great deal of information concerning the toxicity of products can be deduced from their pharmacological and biological properties, as well as on the basis of their structural analogies. On the other hand, theory is insufficient, and the risk too great, to dare expose an individual to a new product without additional testing. A new medicinal substance is never administered to a human being before the molecule's toxicological profile is known. Unfortunately, there is currently no other alternative as reliable as animals. Certain criteria can be predicted but remain insufficient. Three levels of testing are necessary. Acute toxicity studies examine the effects on the animal up to the point where the maximum tolerable dose is reached. Long-term effects can be observed with chronic toxicity studies where an average dose, higher than the normal therapeutic one but not fatal, is administered over several weeks. Finally, reproductive toxicity testing is necessary in order to demonstrate that the substance does not lead to any malformation or genetic modification in progeny, even to the second generation.

As it is quite difficult to directly transpose animal testing results onto man, this information on toxicity is only informative in character. Basic precautionary rules and regulatory authorities' recommendations oblige the pharmaceutical industry to carry out these tests on two different animal species.

The toxicity of a radiopharmaceutical is characterised by two aspects. Firstly, all the radiological risks linked to the absorption of a radioisotope must be taken into consideration. This subject has already been discussed in detail in the chapter concerning radioactivity and radiation, and this toxicity is well-known and well-controlled. Once an isotope's distribution in the organism has been identified, it is possible to evaluate its radiological impact on the organ in which it is retained, and so deduce the maximum dose that can be injected – and which should not be exceeded.

It is perfectly obvious that this injected dose must take the radioisotope's specific activity into account, that is to say the relationship between the activity of this radionuclide and the total mass of the element present. A radioisotope is frequently accompanied by its equivalent stable element. In a way, the radioactive molecule is diluted in an environment containing this same molecule in its stable form. The term "carrier" is used to define this stable fraction.

The second aspect relates to the cold part of the molecule, which becomes insignificant however when compared with the risks associated with the radioactive part of the molecule. In most cases, the toxicological profile of the vector is known, since the molecule is often the product of traditional pharmaceutical research which itself provided all the toxicological data.

The quantities of biologically or radiologically active material injected into a patient are extremely low. For example, the quantity of iodine injected in order to carry out thyroid scintigraphy corresponds to a thousandth of the iodine dose that we absorb daily with our food. The toxicological effects associated with this extra iodine are invisible. This example may be applied to all injected products. Whichever the vector used may be, it is always at a considerably lower concentration level than the point at which the first signs of toxicity are likely to appear. This affirmation is true to such an extent that it is possible to envisage labelling well-known toxic substances with a radioisotope in order to inject them into man, knowing that the toxicological risk remains fully under control. The side effects linked to the radioisotope grafted onto the molecule will always be greater than the intrinsic toxicity of the vector, at the doses used. Consequently, the number of toxicology tests to be performed on animals before injecting in man is considerably reduced compared to conventional pharmaceuticals.

All that remains to be confirmed is the absence of abnormal immune reactions (allergies), and, in the case of antibodies, the formation of human anti-mouse antibodies (HAMA), human anti-chimerical antibodies (HACA), or human antihuman antibodies (HAHA).

With these findings, the development of new nuclear medicine products can be envisaged on a completely different level: a number of molecules studied in the context of developing new pharmaceutical products display remarkable biological profiles (very high level of binding), but unfortunately have to be rejected due to their high toxicity. Due to their specificity, they make excellent vectors for future radiopharmaceutical molecules, as their toxicity level becomes increasingly insignificant. The major pharmaceutical companies' research centres count many abandoned molecules in their drawers which could serve as a basis for new radiotherapy products' families.

Insofar as a radio-labelled molecule can be seen directly through the organs, its pharmacological evaluation is also accelerated since all the information is visible via images of a complete animal. Tests are carried out more quickly, they are less numerous, and the data obtained can be used immediately. In the case of a traditional pharmaceutical substance, it takes two years on average to obtain the necessary data before moving on to man. This same information is available within barely six to nine months with radiopharmaceuticals.

V. PHASE I CLINICAL STUDIES

The term clinical studies covers all the tests carried out in humans. With the help of several healthy volunteers, phase I studies attempt to show that this new product is harmless.

On the basis of the data collected during the above-described pre-clinical studies, whether or not to carry out human testing is one of the most important decisions that needs to be made, for three reasons. Firstly, injecting a product into a human being for the first time is not a trifling matter, and the whole company's responsibility is at stake. This decision is taken with the participation and support of toxicologists and medical experts specialising in this field. Secondly, doubts concerning the toxicology results or the effectiveness of the molecule may still exist, and it is sometimes preferable to confirm these

results with supplementary preclinical studies. Finally, committing oneself to the clinical phase – involving humans for the first time – is the costliest development phase. The right molecule must be found, and the right target must be hit first time.

Before even finding out if the new molecule has a significant therapeutic advantage, both the fact that it is harmless to humans and an idea of the maximum dose that can be tolerated need to be confirmed. At this stage, only data obtained from animals is available for reference. This first study must be carried out on healthy male volunteers. The main objective is to detect any undesirable or even harmful effects of the molecule in humans which were not detected in the animal. In general, doses a hundred times lower than those that caused side effects in animals become therapeutic doses. The clinician starts by giving even lower doses to the volunteer, increasing them progressively. Regular listening to, and constant monitoring of these volunteers help establish the dose at which these first symptoms systematically appear, information that the animal could not communicate (pain, dizziness, migraine, inadequate taste, etc.). In general, this dose also corresponds to the maximum dose which should not be exceeded. In order to limit other side effects as much as possible, these first tests do not involve women, children, elderly people, or people who are too weak. Paradoxically, drugs intended for women only, such as the contraceptive pill, are also tested on men in the first instance. The formulation used (gel, capsule, pill, patch, injection, or suppository) will remain the same during the entire study, even if a few more minor changes are still necessary at this stage.

Healthy volunteers are selected by a team of specialist clinicians on the basis of very strict criteria, including their non-participation in other similar studies in order to avoid an unrecognised interaction with other molecules in the course of development. Tests are carried out in a hospital that is fully equipped for intensive care. Volunteers in phase I clinical trials are remunerated for their active participation

in these experiments. Their status is protected by law and by the Helsinki agreement.

In general, the results obtained on the basis of a dozen participants are sufficient to decide whether to move on to the next phase. Along with collecting subjective data from the volunteers themselves, a number of parameters are recorded (electrocardiograms, electroencephalograms, etc.) and analysed (blood, urine, faeces, saliva, sweat, etc.). Two or three optimal doses are deduced from these studies, as well as the maximum dose which should not be exceeded. Finally, the type of formulation used is confirmed.

VI. PHASE II CLINICAL STUDIES

As they move on to clinical phase II, clinicians aim to demonstrate that the product has a positive effect on the pathology, and seek to estimate the ideal dose that should demonstrate the new drug's effectiveness.

Whereas recruiting a dozen of volunteers through the press for a phase I clinical study is easy enough, it is more difficult to start an experiment with people who are sick. Phase II consists of confirming the effectiveness of the new drug on a small number of patients – generally about forty – who have agreed to take part in the experiment. The study is carried out in collaboration with physicians on the basis of a very strict protocol developed jointly. The first study, which generally takes place in hospital, takes into consideration most of the reference parameters used in phase I (heart, neurological, biological), but its main objective is to analyse the evolution of the illness.

Experience shows that, depending on the environment, in some cases a clear improvement in the patient's condition is noted, even in the absence of treatment. This is called the placebo effect. When patients feel cared for, have confidence in the care-providing team, and believe in the effectiveness of the treatment, their physical

condition may improve to such a point that the drug may seem to be of no use. Conversely, a failing morale, a depressed psychological condition, misunderstanding the intentions of the people with whom patients communicate, and a pessimistic environment may aggravate a situation, even when the best of treatments is being applied. This is the nocebo effect. These effects may be very significant. They account for more than 40% in the treatment of all gastroenterological problems and ulcers in particular, and for more than 80% in the case of neuropsychological problems. In other words, this means that an antidepressant drug for example will only have a therapeutic effect on the remaining 20% of patients, and that the administration of sugar combined with the therapist's conviction could practically improve the condition of 80% of the other patients. As it is impossible to test all these psychological parameters, physicians responsible for clinical studies have had to incorporate this factor into their protocols.

Each study is carried out using a control group. This reference group is selected following the same criteria as for the group to be treated, and it receives an inactive form of the drug which is in all other points identical to the medication being tested, called the placebo. Neither the patient, nor the doctors, nor the care staff know who will or will not receive this drug. Selection is random, and the names of the patients who have really been treated will not be revealed until the very end of the study, when the results are collated and analysed. This is a double blind study which is the only way to bypass environmental influence on the treatment.

However, it should be noted that studies using a placebo do not apply to serious pathologies, as stopping an effective treatment would not be ethical. It is obvious that physicians do not allow the life of a patient to endangered. The traditional treatment is maintained for the two groups of patients, and the new treatment is given to one group only as a supplementary course, to see whether it brings additional effectiveness.

In parallel to the verification of the effectiveness of the treatment, physicians try to determine the ideal dose. In order to do this, they may need to separate the group being treated into sub-groups to which different doses are given. If results show that another dose could have been employed and would have led to better results, or that a change in formulation could have been more effective (gel capsule instead of pill), the study is started again. Phase II results determine whether the last clinical phase can be undertaken.

The length of the study depends on the parameters being followed. As it is about effectiveness, physicians will above all seek to find out if the product acts quickly and effectively on the illness. In some cases, results are obtained in a few days. In oncology, the main objective is often linked to the patients' survival. Therefore, they are monitored for a long period after the treatment has ended, generally equal to the average life expectancy for this category of patient.

Diagnosis radiopharmaceuticals come into the first category with very fast results. The image acquisition is immediate, and can be interpreted within a few hours. Physicians only have to wait, at the very most, for additional parameters – biological analysis for example – in order to confirm the test's validity. In the case of diagnosis, the placebo effect is rarely mentioned. On the other hand, the protocol is written in such a way that the physician in charge of the evaluation can only read the images in a blind form, without knowing the patient or their history.

Therapy radiopharmaceuticals come into the category of products requiring a long period of analysis before their effectiveness is confirmed. Double blind treatment is particularly difficult and little used, because the standard reference treatment rarely consists of another radioactive treatment. It is quite easy for patients to identify when they are being injected with a radioactive substance, if only because of the special environment in which the test is performed. On the other hand, metabolic radiotherapy products are only presently administered to patients for whom all other traditional methods of

treatment have unfortunately failed. This complicates the organisation of these studies, and the clinicians who write the protocols have to bear this in mind. Nevertheless, taking into account the fact that it is possible to verify the product's distribution by means of imaging techniques, results are obtained more rapidly. Their analysis is also accelerated and, due to the precision of the method, the overall number of patients to be treated can be reduced.

As injecting radioactive products into healthy volunteers is neither authorised nor recommended for ethical reasons, Phase I and II clinical studies are combined together in the case of radiopharmaceuticals. A first Phase I/II study follows the protocol of a conventional Phase I study, but volunteers are replaced by patients. Side effects studies are directly carried out on those patients who will not necessarily benefit from the efficacy of the drug as doses remain very low, but this reduces the number of patients involved in these phases accordingly. Clinical phase III is consequently carried out sooner with a positive impact on the overall cost of the clinical development of radiopharmaceuticals.

VII. PHASE III CLINICAL STUDIES

Phase III studies demonstrate the actual effectiveness of the product in a large number of patients, along with its superiority as compared to the current reference treatment and the absence of any widespread side effects.

This phase is a key stage in any development because products are very likely to be marketed one day. One molecule in five or six passes the phase I stage. This proportion is the same for phase II. A radiopharmaceutical has one chance in two or three of passing the first clinical stages. Phase III serves to confirm both the declared effectiveness and the absence of side effects in a much greater population. Depending on the indications, a clinical phase III study requires from 500 to over 4,000 patients. Two distinctly parallel studies need to be carried out, which are called pivotal studies. If

the product's effectiveness really is demonstrated in the course of phase II, a placebo group is no longer necessary. On the other hand, in order to be marketable at a later stage, the product must show a clear advantage over the commercially available reference drug at the time of the study. Therefore, clinical studies are constructed in such a way that the results of a group receiving the new drug can be compared with those of a reference group being treated with the traditional products (preferably the best on the market, called "gold standard"). In order to avoid any external influence, this study is also carried out as a double blind. Formulation scientists are sometimes obliged to repackage commercially available drugs, in order to make them look like the new treatment under evaluation.

The final product used in this study must be in the same medicinal form as when it eventually gets marketed. Chemists and formulation scientists take advantage of the phase I and II period in order to develop a method of synthesis, a final formulation, and a method of production that can no longer be changed, except by carrying out the phase III study again.

Taking into consideration the number of patients involved in this phase, it is also the costliest. About one third of the overall cost of developing a drug is absorbed by this clinical trial phase.

In parallel, to anticipate certain questions which are bound to be soon asked by the authorities, and to ensure the safety of the product for a wider public, some additional phase I level clinical studies will be carried out. The term phase I does not always correspond to the first stage, nor is it automatically linked to the involvement of volunteers, but it defines the number of parameters to be monitored in an extremely rigorous fashion. Depending on the circumstances, the drug's effect on certain sub-groups of patients is studied – such as individuals suffering from liver or renal deficiency, or patients of a particular type, for example suffering from obesity or diabetes. Sometimes the harmless nature of the drug in relation to elderly patients needs to be confirmed

and, if the product is to be given to children, a study needs to be carried out in a paediatric environment.

Another important mandatory complement consists of including a proportion of individuals corresponding to the ethnic minorities of a particular region within the group of patients participating in a phase III clinical study. It may happen that certain treatments are less effective in people of a different ethnic origin. In order to demonstrate the contrary, a study carried out in France should include about 10% North Africans, and the same proportion of black people in the United States. The Japanese Government requests that a full phase III study be carried out, preferably in Japan with an Asian population. Since 2015, the Chinese government has been requesting similar Phase III data on Chinese patients.

American regulations oblige the industry to demonstrate the product's effectiveness in two distinct phase III studies, commonly known as the pivotal studies. In order to be of benefit at the marketing stage, these two studies slightly differ in terms of patient selection, expected results criteria, and reference products. Patient distribution is revealed at the end of the phase III study. This crucial stage in a product's life, called the unblinding, gives confirmation of the sub-group in which the drug proved the most effective. Only then is it possible to find out whether the product is effective or not in comparison with the control group. This stage virtually signs either the product's marketability, or its death warrant. At this stage, the company will have already spent several hundred million euros.

Due to the particular nature of radiopharmaceuticals, the number of patients included in a phase III study is relatively small and can be limited to a few hundred patients. This parameter does not affect the time involved, but it has considerable impact on the cost. In consequence, a company developing radiopharmaceuticals can develop a product aimed at a much smaller population, and thus target illnesses that are a little less common.

DATA PROTECTION

A new drug is only of value to a company if the latter can keep a monopoly over its product and exploit it for as long as possible. The only effective protection consists of holding a patent. Any new molecule displaying original pharmacological properties can be protected for 20 years, to the inventor's advantage. During these 20 years, no other company can exploit the invention in the country where the patent was filed without authorisation from the patent owner. 20 years seem both long and short. Indeed, once the 10 years required for the product's development are deduced, the research's results must be exploited and bear fruit within 10 years only. For, after this period, the product will enter the public domain to become a generic product, and any sufficiently well-equipped company will be allowed to market it without having to spend any of the investment initially required for its discovery. Patents are applied for as late as possible, because each year gained as regards the patent date is an additional year of competition-free sales. On the other hand, waiting too long is very risky, because if the niche is profitable the molecule may in the meantime be discovered by a rival team which could then apply for a patent itself. The actual process of applying for a patent gives an additional year of confidentiality to inventors, thereby allowing them to improve their discoveries. The patent is then assigned for publication approximately 18 months after the initial application was made. A personal patent may be invalidated if the same molecule appears in a competing patent which was applied for prior to this period. During this time, research efforts will have been undertaken for nothing.

VIII. REGULATORY ISSUES AND REGISTRATION

If the results are conclusive, the company confirms its interest in marketing the product. Between 8 and 10 years will have elapsed since the day when it was decided to start this new project. A marketing authorisation application is made to the competent health authorities. This wholly comprehensive dossier covers all the information linked

to the new product, from its manufacture to every observation collected individually from each patient or volunteer while it was being developed. The final document – namely the NDA or New Drug Application – represents tens of thousands of pages that need to be collected, checked, analysed, and summarised. Obviously, this laborious task must be carried out concomitantly to the work's progress. But the results synthesis can only be done once the dossier of the last treated patient has been analysed.

After pagination, the dossier can be photocopied and the hundreds of kilos of paper sent to the relevant authority. For several years now, an electronic copy (CD-Rom) must also be supplied to the authorities for faster data processing and analysis.

As far as possible, a pharmaceutical dossier of this type is filed with the three major regions corresponding to the three major world markets. For Europe, a single dossier must be provided and filed with the EMA (European Medicines Agency) in London. The FDA (Food and Drug Administration) decides on American dossiers (United States), and the Koseisho deals with Japanese ones. Given the complexity of the work, it is preferable to file the dossier with one of the major regions (Europe or the United States) before filing it with a second region in order to be able to provide a corrected dossier and limit the questions, once exchanges with the first agency have taken place. Dossiers are usually only filed in Japan in third place, due to this country's protectionist policy which leads to additional and extremely severe constraints – in particular the need to complete the dossier with clinical data generated with Japanese patients.

The agencies must be warned several months in advance of the arrival of a new dossier, so that they can organise themselves and start working on it as soon as the documents are handed over, along with payment of the evaluation costs (about 280,000 euros for the EMA in 2016).

The authorities undertake to analyse the dossier within a given deadline. Payment of the charges equates to a contract stipulating

very precise due dates as regards the work they have to provide. Initial comments and questions must be returned on a set date. An additional clinical study may be requested in certain extreme circumstances. In this case, the project may be postponed for several years.

In practice, an average of 18 months should be allowed between filing the dossier and obtaining the marketing authorisation. After this authorisation is obtained, due to the workings of recognition between countries, other applications will be filed with countries which are not covered by the three major markets. Up to 3 years can easily pass before a drug first marketed in the United States is authorised in Europe, and vice-versa. It can even take up to 10 years for it to become available in Asia or South America. At this stage, procedures are the same for pharmaceutical and radiopharmaceutical products.

IX. MARKETING

Obtaining an authorization is the most important stage before marketing. Nevertheless, several administrative barriers still have to be overcome. In the case of a product intended for hospital use, negotiating its price and obtaining its reimbursement rate require local authority approval, country by country. These procedures are time-consuming, and it takes another few more months before the medicine can be prescribed and patients can benefit from this new treatment.

As radiopharmaceutical products are only sold in a hospital or clinic environment, price discussions are very limited. Then, even if a good sale price has been negotiated, the sales volume is directly linked to the budget allocated to hospitals by the local government, thus limiting the industrial income.

More than 10 years separate the initial decision to break into a new niche from the moment the drug can be sold on the market. Each time reduction in any one of the development stages has obvious economic repercussions. Due to the simplification of some of the stages, and

to the reduced number of patients involved in the development of radiopharmaceuticals, such products can be marketed within 7 to 9 years after the start of the studies. The budget swallowed up in this development remains between 80 and 200 million euros for a radiodiagnostic agent, with an average potential annual turnover of the same level. Radiotherapeutic development costs can reach up to 400 million euros, but with a yearly income potential of up to 5, if not 10, times this level.

X. POST-MARKETING AUTHORISATION AND DRUG MONITORING

As with all drugs, radiopharmaceuticals must be monitored to detect any side effects that may only appear once this type of treatment has been administered to a greater number of patients (pharmacovigilance). In fact, expected side effects with radiopharmaceuticals are extremely rare and of lesser importance, especially when compared with the illness they are supposed to follow up or treat. All this information is collected by the authorities and highlights any possible undesirable or harmful effects of a drug which could not be assessed during clinical studies. Some side effects only appear in a ratio of one in a million, and therefore remain very often invisible during clinical phase III which only included several thousand patients. If the drug is distributed to millions of sick people, dozens of people may be affected by these previously unobserved side effects. It is important to collect and centralise this information. Depending on the seriousness of the effects observed, the drug may even be withdrawn from the market.

A drug may be sold once it has proven effective in a particular sub-group of patients. It is then marketed with this single indication. Physicians soon start to ask for an extension of this indication to another sub-group of the population (another age group for example). In order to be able to sell the product to a wider public, its effectiveness and safety must be demonstrated through additional

studies. The purposes of such phase IV clinical trials – which are only carried out once the drug has been made available on the market – are to explore the dosages suitable for selected subpopulations, to study the different administration regimes, or to check compatibility with other treatments available on the market (and administered at the same time). Undeniably, product prescribing is safer with these studies.

Extending the indication itself, in other words using the same medication to treat an illness for which the drug has not been tested, requires a new demonstration via a phase III clinical study. In consequence, a new dossier must be filed.

SUMMARY

Before it is marketed, a new drug undergoes a development phase consisting of a series of tests, first on animals, then on humans. These tests require ten years of work and an investment of several hundred million euros.

All molecules roughly follow the same development sequence:

- **Chemical synthesis:** after developing the molecule and its synthesis, chemists test it on simple *in vitro* models (in test tubes) in order to check its biological potential for the mechanism of the indication being considered.
- **Pharmacology:** this second stage consists of verifying if complete and isolated organs provide a positive answer to this molecule.
- **Preclinical studies:** the substance is tested on animal models in order to check the positive effect of the substance on a particular pathology.
- **Toxicology:** at this stage, it is important to determine the toxicological risks linked to the substances, at very strong doses as well as at weak doses administered over a long period.
- **Galenic:** the method of administration (formulation) of the future drug is developed.

– **Clinical phase I:** if all the initial tests are positive, this substance can be injected into healthy volunteers in order to check for the absence of side effects.
– **Clinical phase II:** this phase consists of checking the product's potential in the first patients, and above all of finding the ideal usage dose for the treatment to be effective.
– **Clinical phase III:** these trials must demonstrate in a very large number of patients that the drug is effective at the dose recommended in the previous clinical trial without any signs of unwanted side-effects.
– **Registration:** before the product can be marketed, the necessary authorisations must be obtained once the quality of the studies and the validity of the results have been verified by competent experts.

Radiopharmaceuticals are subject to these same development constraints and steps, with the exception of Phase I studies which have to be performed with patients instead of volunteers in combined Phase I/II studies. As a consequence of the imaging technology, some results are obtained immediately (the image itself), and because the quantities injected are extremely low compared to traditional drugs, the whole toxicology study phase can be reduced. Therefore, the overall development period is shortened by a year or two.

Once marketed, the drugs continue to be monitored very strictly (pharmaco-vigilance), and radiopharmaceuticals are no exception to this rule.

8

The Production of Radiopharmaceuticals

The radiopharmaceutical product status is obtained on the basis of very well defined production quality criteria. The final product quality must correspond to the specifications described in the marketing authorization dossier and approved by the various drug agencies. Also, the manufacturing process must be reproducible from one batch to another.

The radionuclides and labelled substances which are produced using a method other than the one officially approved by the authorities, and linked to an approved pharmaceutical manufacturing process, are called "radiochemicals" – which differentiate them from the officially approved "radiopharmaceuticals". During the development process of a new tracer or drug, it is obvious that the substances used bear the status of radiochemical product. Nevertheless, those that are injected into humans in the context of a clinical study are subject to the same type of controls as approved radiopharmaceuticals. Therefore, they must follow the same criteria guaranteeing product quality, to prevent any risk of harming or endangering the lives of patients.

I. DEFINITIONS

Radioisotope decay causes the composition of a radiopharmaceutical solution to change over time, which leads in particular to the increase of by-products. It is therefore necessary to define several measurable parameters, and particularly those informing physicians on the precise quantities of radioactive substances actually injected into patients without a limit of use, the **shelf-life** beyond which the product quality no longer meets approved specifications.

The **specific activity** of the radioisotope corresponds to the ratio between the activity of this radionuclide and the total mass of the element or molecule present. A radioisotope solution is called **carrier free** when only radioactive atoms are present, even in an extremely dilute solution. Specific activity is expressed in becquerels per mass unit. This concept of radioisotopic concentration is essential for labelling vectors. Coupling an isotope with a vector results in a reaction which can only be effective, and returns a very good yield in the absence of competition between hot (radioactive) and cold (non-radioactive) isotopes.

Specific activity should not be confused with **radioactive concentration** (or volumetric concentration). The latter determines the degree of radioactive substance per volume unit (expressed in becquerels per volume unit).

A radiopharmaceutical must be produced in a precise time frame. Taking decay into account, the radioactive concentration is always higher at the end of production than at the time of injection. In order to take transport time into consideration, a radiopharmaceutical is delivered with a certificate indicating the radioactive concentration at a precisely defined time (usually close to the time of administration). One then speaks of the **calibration date** and of activity or dose on calibration, which corresponds to the real dose at the acceptance time by the radiopharmacist. On the basis of this value, physicians can precisely calculate the volume fraction to be taken when the patient is being injected, or prior to the radio-labelling stage. The calibration

date should not be confused with the **expiry date** or shelf-life – important criteria for any pharmaceutical product – corresponding to the time beyond which the solution of the tracer can no longer be used in patients. Decay is accompanied by both a dilution effect and the appearance of new impurities, including radiolysis products and decay-produced isotopes. Stability studies carried out on samples have defined a specific time period at the end of which the product no longer meets its own quality criteria. These parameters must take storage and transport conditions into consideration, particularly storage temperature and any possible interaction with the container and other materials contained in the flask. The expiry date may be extended artificially by adding stabilisers (excipients), but excipients won't actually have any influence on the radioisotope's decay. If a tracer contains stabilisers, these are part of the formulation anyway and described in the approved drug dossier.

II. PRODUCTION OF RADIONUCLIDES

Radionuclides can be produced in several ways, using a reactor, a cyclotron, a linear accelerator, or a generator. It is also possible to extract them from natural sources, decay chains, or fission by-products (nuclear waste valuation).

Two major difficulties limit the production methods. Firstly, handling radioactive substances requires a suitably safe – and therefore very costly – environment. Secondly, nuclear medicine can only use radionuclides of very high purity, requiring optimised methods of separation and purification. Generally speaking, most radionuclides to be used pharmaceutically are easily accessible. In fact, products used in nuclear medicine have only been developed on the basis of radioisotopes that are easy to produce and purify. Nevertheless, their short half-lives require rapid handling, transformation, and distribution. The production and purification parts of the process must obviously be taken into account in the overall period of use, as

the rapid decay constantly generates daughter isotopes which must also be considered as they increase the level of impurities over time.

1. Reactors

Most radionuclides used in nuclear medicine are artificial isotopes. The most usual method of production consists of bombarding a stable isotope (the target) with a flow of neutrons in a nuclear reactor. This neutron condenses with the existing atomic nucleus, thus creating an unstable isotope of the metal used as target.

The most common radionuclides produced in reactors include Lutetium-177, Holmium-166, Tungstene-188, and Phosphorus-32. The sources of radioactivity for radiotherapy, such as Cobalt-60, are also obtained in reactors.

Molybdenum-99 – parent radionuclide of Technetium-99m – may be formed by neutron bombardment of stable Molybdenum-99. The yield from this reaction is very low, and Molybdenum-99 is extremely difficult to separate from Molybdenum-98. The mixture of cold and hot molybdenum can be used directly in the generator (*see below*). This use remains limited because its specific activity, i.e. the ratio between hot and cold material, remains low. Expressed in radioactivity, the specific activity seems very high, but brought down to a quantity level, the mixture contains less than one radioactive atom per several million cold atoms. For generators, it is therefore preferable to use molybdenum which is the product of uranium fission (*see below*).

2. Particle Accelerators

A radioactive substance can be formed by bombarding a stable substance with charged particles in a linear or circular type accelerator. The most frequently used tools are cyclotrons. But whatever the technology used, the same type of radionuclide is formed by the bombardment of an identical target with the same type of charged particles. Only the energy of the beam will influence the type of produced radionuclide and the yields.

Thus, in a cyclotron, charged particles of low mass such as protons or alpha particles are accelerated in a circular trajectory until they reach high energy and high velocity close to the speed of light. These particles are used to bombard a specific target which may be solid, liquid, or gaseous, transforming it into radioactive material. Unlike a reactor, a cyclotron is ideal when the radioisotope formed is a different element than the cold isotope placed in the target. For example,

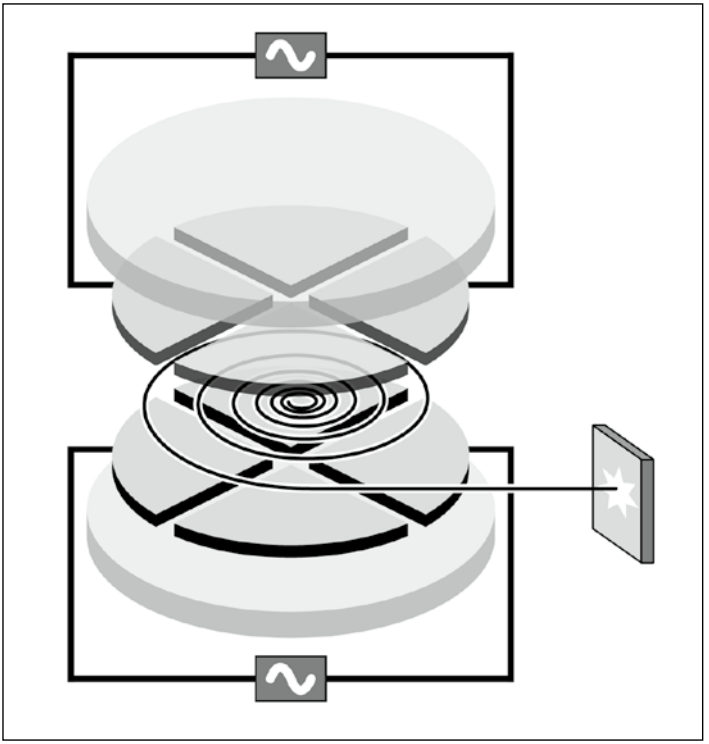

Figure 12 | Diagram of the cyclotron functioning principle: protons generated at the centre of the cyclotron are accelerated in an area under vacuum by means of an electromagnetic field schematised by the four quadrants. When they reach their ideal speed, the protons are directed onto an external target containing the element to be transformed. The nuclear transformation reaction takes place in this target. When the production process reaches an end, the resulting radionuclide is isolated and purified in a radiochemistry cell that is close to the cyclotron unit.

Fluorine-18 is a positron emitter formed from Oxygen-18, which is a stable isotope combined in this particular case with hydrogen to form water. Similarly, Iodine-123 is a γ emitter produced from Xenon-123, a stable gaseous isotope. At the end of the process, the radioactive element can easily be separated from the cold element that served as target, since the chemistry of the resulting element completely differs from that of the starting material.

In a cyclotron, the particles are accelerated in a circular electromagnetic field under high vacuum. When these particles reach a suitable speed, the beam is directed outside the field onto the target to be irradiated. The operation usually lasts from an hour to less than a day, and only exceptionally a few days. Actually, the time of irradiation is close to the half-life. If the irradiation time is longer, then the produced radionuclide can itself be submitted to the influence of the beam and generate new unwanted radioactive by-products. The irradiated target is extracted from the cyclotron by radiochemists in order to be treated in such a way as to separate the radioactive elements from the residual cold matter. Products obtained via a cyclotron have an extremely high specific activity. In fact, the products are virtually pure, but the quantity of material actually available can be counted in millionths of a milligram. Just to give an idea of the amount of radioactive material produced, the total amount of Fluorine-18 generated in the hundredths of cyclotrons active daily and worldwide since the discovery of this radioisotope, and already used to diagnose millions of patients, has not reached one full gram yet. In order to image one billion patients, we need to produce one hundred milligrams of Fluorine-18 at calibration.

Linear accelerators show the property to accelerate particles to the same speed as in a cyclotron over a very short distance (a few meters). Targets and processing of targets are identical as in cyclotrons. So far, linear accelerators have not reached the development of cyclotrons as they have not demonstrated the same level of yields.

Accelerators and cyclotrons are used to produce Fluorine-18, Carbon-11, Nitrogen-13, and Oxygen-15, as well as Iodine-123, Thallium-201, Indium-111, and Gallium-67.

More complex radionuclides such as the alpha-emitters Actinium-225 and, Astatine-211 are also produced in cyclotrons.

3. Generators

A generator is a small device containing a radioisotope of medium half-life which transforms slowly over time into an isotope displaying ideal characteristics for a nuclear medicine application. This "parent" isotope is fixed to a medium which acts as a filter and retains it. When washed with a saline solution, this medium releases the formed "daughter" radionuclide, while the non-decayed parent still remains trapped. Technetium-99m – the most frequently used diagnosis isotope – is produced using a generator. This isotope with a half-life of 6 hours is formed by the breakdown of Molybdenum 99 which has a half-life of 66 hours, and the fraction formed can be collected regularly each day for use on-site. The size of a five-litre can, the whole device is composed simply of the filter column containing the Molybdenum, a pocket of saline solution, and the tubing – the radioactive part being protected by fifteen kilograms of lead. A generator of this type is exhausted in about 2 weeks.

The generator is an ideal tool for the production of Technetium-99m because the latter is involved in more than two thirds of nuclear imaging techniques. The isotopes produced using generators are relatively limited. Nevertheless, there is at least one known example of a generator model for each radiation type on sale or partially in development, including alpha-emitting isotopes. Other currently available generators can produce Rubidium-82, Rhenium-188, and Gallium-68. The precursors or parent radionuclides in these generators are Strontium-82, Tungsten-188, and Germanium-68 respectively. These radionuclides are produced either in reactors or with very large cyclotrons.

4. Fission Products

Many centres processing nuclear waste from fission reactions have access to large quantities of materials considered to be useless. Most of these are by-products of long half-life heavy isotopes used in nuclear power plants. They are stored while waiting for their complete breakdown, which may take thousands of years. Among these radionuclides, there is material useful in nuclear medicine. It is possible, in some cases, to separate them from other isotopes. For example, Iodine-131, Molybdenum-99, and also Strontium-89, are obtained by separating the mixture obtained after thermal induced fission of Uranium-235 in a reactor. Molybdenum-99 is a compound identical to that described in the neutron bombardment method, but much easier to separate from the other radionuclides.

More recently, it was discovered that Lead-212 – one of the decay-products in the Thorium radioactive decay chain – could play an interesting role as a radiotherapeutic; it is currently undergoing extensive development.

III. THE PRODUCTION OF VECTORS AND LIGANDS

Vectors, in other words organic molecules and synthetic peptides or antibodies, are traditionally produced by organic chemists and biologists. Their preparation must follow the production recommendations and constraints applicable to all pharmaceutical substances. The basic rules are set at an international level in the Good Manufacturing Practices (GMP) recommendations. No deviation from the synthesis and purification methods filed in the Marketing Authorisation dossier is allowed. This rule ensures that the final product's quality can be reproduced for each manufactured batch. Indeed, these rules are the same for both pharmaceuticals and radiopharmaceuticals.

A radioisotope can only very rarely be grafted directly onto the vector (covalent bond for halogens such as iodine or fluorine). During

the course of development of the molecule, chemists must develop a method of connection by trapping radioactive metal in an organic cage – a chelating agent – which ensures that the radionuclide is irreversibly attached to the vector. This stage of additional chemistry must obviously follow the same production constraints as does the production of the rest of the molecule.

IV. THE INDUSTRIAL PRODUCTION OF RADIOPHARMACEUTICALS

Unlike drugs manufactured in very large quantities, there is very little difference between the production of radiopharmaceuticals for clinical studies and the routine production for prescribing to patients. There is no possibility of storing radioactive material, and therefore daily production is mandatory. The process used during the clinical trials is almost the same as the process used when the drug reaches the market. Everyday production corresponds exactly to the number of patients to be treated on the same – or following – day, depending on the half-life and the local requirements. In routine production, a few extra doses for testing the product's quality need to be prepared. Therefore, the production unit for routine usage is often identical to the development unit during the clinical trials, if they are not one and the same unit. Taking the short half-life of radiopharmaceuticals into consideration, their manufacture must be repeated each day. It can be compared to a "just in time" production process, subject to external constraints that may cause a real availability problem to patients (manufacturing interruption, transport strike, etc.).

When the production batch is greater than just a few units, it is not possible to check the quality of each unit individually. Several sample vials are reserved for product quality testing. The quality of the whole batch is guaranteed by the reproducibility of the manufacturing method. No deviation from the process or the specification is accepted. The raw starting materials must have been manufactured according to a well-defined method, and they must comply with pre-established

specifications. Quality Assurance ensures that the methods of production and control are properly described and complied with. Quality Control is responsible for checking that the properties of the final product actually correspond to the specifications. These relate to both the composition of the product and its packaging, including the level of impurities and labelling; they also ensure that the product complies with sterility and apyrogenicity (the product must not be potentially held responsible for triggering a fever due to the presence of endotoxins of bacterial origin that cannot be destroyed during the sterilisation cycle, nor eliminated by filtration). The release of batches – therefore the authorisation for the day's production to be sold – is the responsibility of the Managing Pharmacist, as in any other traditional pharmaceutical industry.

The safety aspect in the context of production has so far scarcely been touched on. It is well understood that the most significant difference between development and production concerns the quantities of radioactive substances being produced. Therefore, production areas are equipped and protected accordingly. Handling is carried out in shielded boxes, i.e. manufacturing cells provided with leaded windows and grabs. Technicians are protected by a layer of more than 10 cm of lead, and the cells contain all the material required for production. The staff who manufacture the drug work on one side of this production cell, namely the front, using remote manipulators (giant mobile grabs). They control their work through thick viewing windows made from leaded glass. Operators who work on the other side are responsible for moving all the material required for the manufacturing in and out of these cells via large lead-lined airlocks. All the radioactive matter leaving these cells, including waste, is compulsorily confined in lead protective containers. By way of consequence, none of the operators is ever in contact with a radioactive product, except by accident. It is very difficult to automate this sort of production, and each vial is produced one at a time in an almost artisan fashion.

The routes travelled by the material are arranged in such a way that it is possible to define zones of increasing radioactivity, and in consequence, zones of increasing radiological risk. Thus, front-side technicians can never come into contact with operators at the back during the course of production. Only the latter work in an accidental contamination risk area. Leaving these zones at any time is controlled to the extreme. Each operator carries a radioactivity detector, and must also go through more than one check area before leaving his/her place of work. In principle, radioactivity can only leave the site in leak-proof leaded containers – whether it is a drug vial or waste in sealed drums.

V. TRANSPORT AND LOGISTICS

Several hundred thousand consignments per year – that is several thousand per day – leave production centres for delivery to their final destinations in as short a time as possible, but above all without the slightest incident. No means of transport is excluded, but road and air are favoured. At the end of the production day, dozens of lorries wait to be loaded outside the despatch warehouse exit. Their arrival and departure times depend on the final delivery time, or the plane's take-off time. Generally speaking, the destination hospital should receive the delivery within twelve hours. Ideally, the active product is delivered for use the next morning, as the hospital's nuclear medicine department opens its doors.

Nevertheless, a number of parameters may interfere with the regular operation of these logistics and imperil delivery deadlines: the state of the traffic, customs checks, acceptance of the deliveries by the pilots in command, etc.

Radioactive products of all types are packed in special containers resistant to falling, crushing, fire, etc. This reduces the risk of accidental contamination during transportation; indeed, such incidents are extremely rare. A frequency rate the order of 1 to 2 incidents per

100,000 consignments seems insignificant; still, it is unacceptable and must be considered on a case-by-case basis. Each event has led to the analysis of both the incident and the risk, resulting in further container modifications and general process improvement and, therefore, in higher safety levels.

With the increased risk of terrorism, the hijacking of transportation means for ill-intentioned ends has been subject to deeper analysis by the state security services. Radiopharmaceutical products do not represent hazardous consignments in the event of a hijacking for example, given their half-life and activity. The risk associated with their dissemination or reuse is almost nil. At the very most, the public and journalists might be psychologically impacted due to a lack of knowledge in this field, but there would be no actual healthcare risk.

VI. RADIOPHARMACIES

All products dispatched to a hospital are not necessarily delivered ready to use. Some handling and checks may be necessary, if only to regulate the dose about to be injected. Certain products even require final onsite production. This is the case for all products using technetium delivered in "cold kits", and which must be labelled on-site with generator-produced technetium. In the nuclear medicine department, the radiopharmacist is in charge of completing this preparation. He/she becomes the final producer. Complying with the same safety and quality rules as those imposed on the industry, radiopharmacists make up the various solutions to be injected each morning. Cold kits contain all the reagents that enable the formation of the expected radiopharmaceutical once they are combined with the right quantity of technetium from the generator. Normally, this stage involves simple mixing and possible stirring over low heat, followed by quality checking, but every single step must follow a very strict protocol. The radiopharmacist becomes the local guarantor of the reproducibility of this last stage, and of the final product quality.

The quantities of matter used are so small that traces of air are sufficient to alter the result. All materials used are sterile, but the final product's sterility also depends on the experience of the person handling it. Finally, each handling procedure is different to the extent that it must be adapted to the quantity and concentration of technetium from the generator.

The work of radiopharmacists is not limited to reconstituting technetium kits, but as the use of these products increases, this represents the greater part of their work. They must, however, be capable of meeting every demand from the nuclear medicine department; given the diversity of isotopes used, their field of knowledge is relatively vast. The recent arrival of therapy kits both diversifies and complicates their field of action. In particular, not all departments are currently equipped to handle activities on such a large scale, and some laboratories need to be improved in terms of staff protection level. Specific authorisation needs to be requested department by department. In most countries now, the authorities have given the resources to set up a system for auditing and monitoring these hospital units.

THE PATIENT IN THE HOSPITAL

Nuclear medicine departments located within a hospital are hardly any different from other departments from a structural point of view, and, if they are not really paying attention, patients can leave without ever having noticed all the security aspects that have been implemented. It often happens that cardiac patients come out of scintigraphy without realising that they were injected with a radioactive substance. For the uninitiated, it is even more difficult to distinguish a SPECT camera from an MRI one. And inside a hospital room, no-one is able to estimate the thickness of the walls and their lead content. However, signs in the form of clover leaves as a reminder of the presence of radioactivity are everywhere, as are the various protective elements for staff (airlocks, windows, walls, lead-shielded syringes, individual rooms, etc.).

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and days following injection or absorption. One can consider that the radioactivity has faded to almost normal levels after about 10 half-lives, so 20 hours after injection of a fluorinated compound, and two and a half days after injection of a technetium-labelled agent.

VII. NUCLEAR MEDICINE CENTRES IN THE WORLD

The global world market for nuclear medicine reached 4.3 billion US$ in 2015. This market is expected to reach between US$ 14 and 25 billion by 2030 depending on the real impact of radiotherapeutics.

Few companies market contrast agents (X-ray, MRI, and ultrasound) together with nuclear medicine products worldwide. Approximately 70 companies sell radiopharmaceuticals on a regular basis, but 10 companies with income above US$ 100 million control about 85% of the market: Bayer (origin Germany/major world market), Cardinal Health (USA), FujiFilm RI Pharma (Japan), GE Healthcare (USA/world), IBA Molecular (France/Europe) which recently (2017) merged with Mallinckrodt (USA/world which became the new company called Curium Pharma), Lantheus Medical Imaging (USA), Nihon Mediphysics (Japan), Nordion (Canada/world), Siemens Healthcare / PETNet (USA/world) and Triad Isotopes (USA). Several smaller companies are local companies or have become specialised in a limited number of products – and sometimes only one, FDG – but do not compete in terms of turnover with the companies showing the above-mentioned figures: AAA (France/Europe), Bracco (USA), Cyclopharma (France), Eckert and Ziegler (Germany/Europe), Eczacibasi Monrol (Turkey/Middle East), Jubilant Draximage (USA), Zevacor (USA), etc. In fact, the majority of the FDG manufacturing centres are run by one-site company structures or are state laboratories, while SPECT products are distributed via local radiopharmacies which are sometimes associated in a network. These radiopharmacies are supplied with radiopharmaceuticals from the above-listed larger companies.

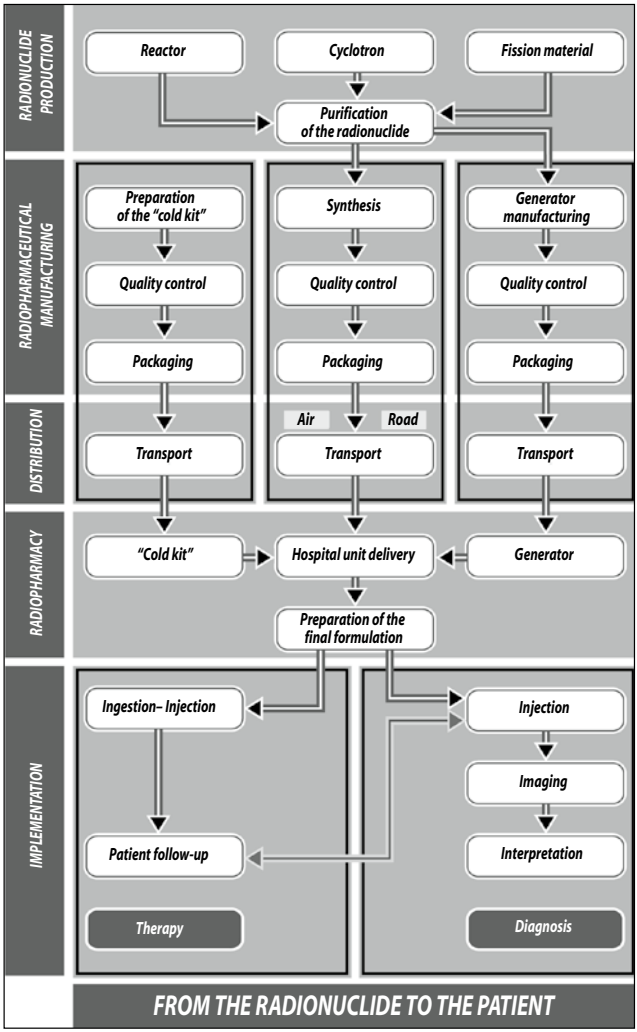

Figure 13 | The availability of a diagnosis or therapy radiopharmaceutical drug requires the initial production of a radionuclide that will be transformed into a radiopharmaceutical, in an industrial environment that complies with all pharmaceutical quality criteria and nuclear safety rules. It will then be packaged and transported to the hospital following these same quality and safety standards. The constraints of short half-lives add an extra difficulty, as the process must be scrupulously respected for risk of losing the final product as a consequence of delay.

Public and private nuclear medicine centres need an official authorisation to handle radioactive products. In developed countries, the ratio of nuclear medicine units is about one centre per 250,000 inhabitants. These centres are located within university hospitals, cancer treatment centres, and public hospitals or private clinics. They must be authorised to handle non-sealed radioactive sources (solutions for injection or capsules for oral administration), and are equipped with dedicated beds in shielded rooms (leaded walls, specific waste treatment units, etc.). On average, each nuclear medicine unit has access to two SPECT cameras.

PET imaging centres are nuclear medicine units equipped with one or more dedicated PET cameras. Each centre is linked to a Fluorine-18 manufacturing unit (cyclotron) located on site or at a driving distance of less than two to three hours. In a well-equipped country (e.g. USA, Germany, France, etc.) cyclotrons are located in such a way that the whole territory can be supplied with FDG. By way of consequence, the limitation in the number of diagnosed patients in those countries is rather linked to the number of cameras, and not to the number of cyclotrons. Most of the developed countries have reached a sufficient level of equipment to allow access to the PET modality (at least FDG) to all of their patients, and are equipped with a sufficient number of cameras. Even if some countries such as Canada or UK started to implement equipment at a later stage, the only remaining areas that still need further growth are located in Africa, South America, India, and smaller Asian countries. There is also a need in Eastern European countries and in the majority of the islands, including Iceland.

Of course, this technology's development in a specific country is a highly political decision that must be integrated in the overall health management structure (cost and reimbursement), as it has a serious impact on the country's health budget. Only very recently, Russia and the People's Republic of China have decided to implement PET at a larger scale; these two big countries alone represent a high market growth potential for the next five years.

By the end of 2016, the number of implemented SPECT cameras worldwide can be estimated at about 24,000. In terms of PET units, the level of equipment depends on each country's priorities. The number of implemented cameras was estimated at about 5,600 by the end of 2016. These PET cameras must be associated to cyclotrons for the local production of Fluorine-18. More than 1,200 cyclotrons have been built over the world and are still operating, but if one deduces the units mainly used for research purposes, about 800 are estimated to be pharmaceutical units operating daily to supply the above-mentioned cameras with radioactive PET tracers. Nowadays, more than 4 million patients are estimated to benefit from PET each year – and probably 50 million from SPECT.

Most countries have reached a consensus on the number of public PET cameras to be implemented on their territory. By 2000, a common accepted figure was one camera per million inhabitants. This ratio is slowly increasing, and was closer to 1 per 500,000 in 2016 – which is an acceptable ratio compared to the needs in oncology. Of course, this number of cameras would become a major limitation should PET cardiology and PET neurology develop, and new investment would be needed both in terms of cameras and cyclotrons.

Nuclear medicine is a speciality with which the public is not well acquainted. This is mainly due to the fact that civil use of radioactivity, even for medical use, has not really benefited from advertising in the past. Patients are mostly aware of this technology through a single modality, namely myocardial perfusion scintigraphy, and they are only beginning to hear about PET and FDG. But even in this case, very few patients associate this technology with radioactivity. There is an obvious confusion with external radiotherapy whenever radiotherapeutics are mentioned. When MRI (Magnetic Resonance Imaging) came on the market, physicians preferred to remove the word 'Nuclear' from the exact denomination of the technology, which is NMR (Nuclear Magnetic Resonance), even though (or maybe

because) this modality is a non-radioactive imaging technology. However, it has never been proven that the use of the term 'nuclear' in medicine is considered as detrimental. Patients majorly trust their physicians regardless of the proposed technology.

Limitations for patients clearly include the access to suitable equipment, and the lack of trained staff. In order to accelerate the decisional process, patients are often guided toward another imaging modality, which obviously does not provide the same level of diagnosis information.

Beside the lack of equipment, another problem must be solved very soon: a new generation of well-trained nuclear physicians will be needed in every country, and this training period will take much longer to complete than buying additional cameras, or even building new manufacturing sites with cyclotrons. There is an urgent need for young nuclear physicians, oncologists, neurologists, and cardiologists with a good knowledge of nuclear medicine, partly because most of the currently handling physicians are to retire soon. It seems that PET started to bring a new lease of life to this specialty with a whole new generation of physicians getting involved in nuclear medicine, but the great change will come with the introduction on the market of theranostics, i.e. therapeutics or even radiotherapeutics supported by radiodiagnostics.

SUMMARY

Radiopharmaceutical products are based on a non-radioactive fragment, the **vector,** combined with a **radionuclide**. Vectors are prepared via any conventional method known by the pharmaceutical industry.

Radionuclides can be obtained in diverse ways:

– direct preparation using a dedicated **cyclotron** or **accelerator**;
– extraction from a **generator**, itself loaded with a parent isotope originating from a cyclotron or reactor;

– irradiation in a **reactor;**
– reuse or purification of nuclear waste and decay products from another source (fission).

Before they are introduced on the market, radiopharmaceuticals are subject to very strict quality testing, in fact identical to that required for conventional drugs.

The complex nature of radiopharmaceutical use is above all linked to the half-life of the radionuclides; it requires special infrastructure and logistics which become even more complex when radiolabelled tracers such as fluorinated products with a half-life of less than 2 hours must be distributed at remote hospitals.

The infrastructure required for administering radiopharmaceuticals in a hospital environment is just as sophisticated. All these environments are subject to regular monitoring in order to preserve biological as well as nuclear safety, and as such they necessitate highly qualified staff.

The future of the technology looks promising; but it will only develop as and when new cameras and treatment rooms are installed, and will need a new generation of trained physicians and nurses.

9

The Future of Nuclear Medicine

The market introduction of the first effective targeted radiotherapy treatments brought a new dimension to nuclear medicine. With the exception of their use in radio-synovectomy, in thyroid cancer treatment (highly efficient), and in reducing cancer pain (limited use), nuclear medicine tools were, until now, more widely used in diagnosis imaging. The introduction of peptide receptor radiotherapy drugs demonstrates additional potential, while the concept of radiotheranostics introduces a new dimension in this field. During the past fifteen years, the introduction of hybrid imaging tools and the combination of different– albeit complementary – diagnosis techniques has given new impetus to this technology, thereby allowing better pathology definition, better patient monitoring, and above all, better treatment direction. A new avenue is also opening up with the arrival of individualised medicine in which imaging plays a key role. With theranostics, a treatment is almost guaranteed to work for a specific compatible patient. Confirming a therapy's suitability for a subgroup of patients becomes much easier with these new tools, via a simpler patient selection which in turn ensures increased treatment effectiveness. It will eventually lead to globally reduced health costs;

indeed, non-responders to a therapy will not be treated with such expensive drugs, for they will be inefficient anyway.

I. HYBRID IMAGING TOOLS AND EQUIPMENT EVOLUTION

The combination of conventional imaging tools (CT, MRI) with nuclear medicine imaging tools (SPECT, PET) provides a solution for locating small tumours. The first approach dates from the summer of 2000, when medical imaging devices manufacturers provided physicians with tools allowing them to simultaneously obtain a both functional and anatomical three-dimensional image. In previous years, researchers had tried to compensate for this lack of resolution in scintigraphic images by acquiring two consecutive scans, one after injecting a radioactive tracer, and the other using X-ray or magnetic resonance imaging techniques. Although computerised data processing has made a considerable leap forward, the complexity of superimposing images of patients who were moved from one table to another between the two scans limited this technique to research applications, and remained totally disproportionate for routine implementation. The arrival of mixed SPECT/CT or PET/CT scanners can be considered to be a real revolution in the field. Hybrid PET/MRI tools took another ten years of development, and only came on the market in 2012. Compared to PET/CT, PET/MRI remains a very expensive tool, and still needs to demonstrate an advantage over existing hybrid imaging techniques to justify the price difference. New applications have recently started to show some of this hybrid modality's advantages in very specific indications.

Today, four large companies dominate the world market in medical imaging equipment: General Electric Healthcare, Philips Medical Systems, Siemens Healthineers, and Toshiba. In fact, by the end of 2016, Canon acquired the Medical Unit of Toshiba and became the fourth largest player in this field. Smaller companies still

exist, but a large number which tried to compete with the four giants in special niches were taken over one after the other in the past years. In October 2003, General Electric took control of Amersham Health, the world market leader for imaging products, thus creating the first group capable of offering both the tools and the imaging products. By acquiring the company CTI (cyclotron manufacturing) with its PET radiopharmacies network, Siemens entered in the same merger strategy. Philips and Hitachi still remain equipment companies without any pharmaceutical activity.

New technologies in hybrid SPECT/CT were introduced in 2012, giving a new boost to SPECT. With the development of new PET cardiology and neurology tracers, dedicated smaller cameras for heart and brain are likely to reach the market soon.

A number of new tracer-developing approaches are based on radionuclides emitting a positron particle and a gamma ray simultaneously, i.e. the production of three photons at once. Special PET/SPECT equipment will be needed, but both tracers and cameras are currently at the animal stage development. At a later stage, these three-beam cameras will also be combined with MRI or CT.

II. INDIVIDUALISED MEDICATION AND THE DEVELOPMENT OF THERANOSTICS

The increase in medical knowledge has contributed to the creation of specialties that are very specific, since one physician alone is no longer capable of knowing everything about human biology and medicine.

Today, for each diagnosis – and therefore for each pathology – there is a corresponding specific treatment. Illnesses themselves have been divided into sub-classes, each with its own therapeutic protocol.

Nevertheless, although these protocols have demonstrated their effectiveness in large groups, there are certain patients who do not respond to an otherwise ideal treatment.

These patients' lack of response to a given treatment is linked to specific types of resistance, or to an absence of responsiveness inherent to their own genetic heritage. In the same way that there are populations who transmit disorders from generation to generation, other types of individuals hand down their resistance when facing certain external attacks. Metabolic processes also differ from one population group to another, and some patients transform drugs which were administered to them faster than others, thus making the treatment less effective. These individual differences seem to be directly linked to a specific genetic heritage as well.

A cancer patient resisting an initial treatment could be offered a second treatment after several weeks or months of inefficient therapy, and even a third one later again. The cancer continues to develop during all this time, and when an appropriate treatment is eventually administered, it is sometimes too late for it to be effective. It therefore becomes urgent to find a method that can determine well in advance whether patients are going to respond positively or not to a specific treatment, even before it is administered. This is the role of theranostic tests. This word was coined by combining the terms 'therapy' and 'diagnostic' (diagnosis). It could be explained as being a method of diagnosis and selection of a patient (and not a disease) with a view to a particular therapy. While the objective of a diagnosis is to identify the illness from which the patient is suffering, theranostics must determine the treatment best suited to heal this individual as quickly as possible – in other words, define positive responders to a therapy.

The concept goes even further: depending on the response to the theranostic test, it should be possible to predict the chances of healing with a specific treatment, to calculate the exact doses required, and to monitor the patient in the remission phase. Treatment then becomes individualised because it is directly linked to the patient's genetic heritage.

In 1999, herceptin – a drug used in breast cancer therapy – was the first example of a treatment based on this concept. The American

administration only authorised the sale of this product provided it was applied only to patients who demonstrated the presence of a herceptin receptor. In this case alone, treatment was likely to be effective. This is still a long way yet from the selection of patients on the basis of their genetic heritage, but this example is sufficient to show that by limiting treatment to a sub-population, its effectiveness is almost guaranteed. Conversely, non-responders to the test should seek other therapeutic methods without wasting their time with a protocol including herceptin.

In general, the pharmaceutical industry is making slow progress in this field, for the simple reason that selecting sub-groups of patients inevitably leads to a reduction in the population to be treated, and therefore to a reduction in turnover. The investment being the same regardless of the size of the targeted group of patients, this is not the direction in which the major groups want to invest. On the other hand, small companies could launch themselves more easily into this battle, by way of orphan treatments *(see below)* which are less costly to develop.

Nuclear medicine has an important role to play in this field. Before even targeting the selection of patients on the basis of their genetic heritage – their DNA or RNA could of course be imaged by labelled substances – it is possible to envisage the display of the distribution of small substance quantities in the sites to be treated. If patients do not show an ideal diagnosis drug distribution, it is not worth inflicting an ineffective treatment on them, providing it has been demonstrated that the drug accumulates in the same sites as the imaging agent. As nuclear imaging allows for a sub-group of patients to be selected, this technology is considered to be a theranostic method. In the context of legislation on orphan drugs, combining theranostic products with diagnosis and therapeutic products opens a fast track for nuclear medicine. Most of the new radiotherapeutic approaches are now based on this approach, and it seems that, in oncology at least, the development of new chemotherapeutics will also follow this trend.

III. ORPHAN DISEASES AND ORPHAN DRUGS

Taking the high cost of developing a new drug and the less-than-philanthropic character of the pharmaceutical companies – and above all of their shareholders – into consideration, legislators have had to set up a system that encourages some laboratories to take an interest in less profitable diseases. These orphan diseases only affect a very small part of the population, and allocating financial resources to this field is only of interest if there is a guarantee of a minimum return on the investment. For several years now, a specific law has been giving companies certain advantages, such as an exclusive market right, if they develop a drug corresponding to the definition of an orphan drug. Such laws have been voted over the past years in the USA, in Europe, and in Japan, and have been implemented in several countries since as early as January 2000.

A drug becomes orphan if it is intended for the diagnosis, the prevention, or the treatment of a disease affecting less than five persons in ten thousand within the European Community. It must be developed for treating a serious disease or one that is incapacitating, and it would most likely not be marketed without incentive measures. It is obvious that this drug must also prove to be superior to any other known available treatment. In some countries, this definition also covers diseases that are very rare in the country itself but which affect millions of people in Africa, and for which research efforts remain limited due to a lack of financial capacity from concerned customers, patients, and countries.

Taking the development costs of a drug into account, therapy for an orphan disease is extremely costly anyway and political support becomes a key issue.

Dossiers of new drugs filed in the context of this procedure benefit from accelerated processing, reduced or even no taxes, and exclusive marketing rights for 10 years. In addition, the dossiers are reduced in size compared to those for drugs targeting a wider population. Dossiers are centralised in Europe; in other words, their applications

are immediately extended to all member states. Orphan drugs may benefit from other incentive measures taken locally to promote research, development, and marketing, and some Health Agencies have undertaken to assist companies in developing their product and in preparing their dossiers. More particularly, research measures in favour of small-to-medium-sized companies have been set up.

Initial applications processed by the European Medicines Agency since these texts came into force have to do with drugs intended for genetic diseases leading to early death, the treatment of cystic fibrosis, certain rare cancers, diseases for which the only therapeutic option lies in a transplant, and above all cancers for which all known treatments have failed.

These last examples become significant in the context of metabolic radiotherapy. Not only is this technology in the process of demonstrating that, in certain circumstances, it is capable of compensating for the deficiencies of traditional therapies, but with the new legislation innovative products should reach the market faster since all the concerned indications fall within the context of orphan diseases.

It is true that, to date, the therapeutic applications of nuclear medicine techniques are limited by the environment in which they have to be conducted. As long as it is possible to demonstrate on a larger scale that this technique can be a substitute for chemotherapy for example, it is obvious that the applications will exceed the framework fixed by the legislation concerning orphan diseases. Legislators have already foreseen these circumstances, allowing for traditional drugs to backtrack and re-enter the development framework. Taking a widened market into consideration, a company is assumed to receive greater profits than initial forecasts. It will therefore have the necessary financial resources for additional studies, which will in turn minimise the risks to patients as these risks increase proportionally with the population growth.

This law has helped to promote the development of nuclear medicine products by small companies which do not target the world

market in its widest sense. However, very recently, conventional pharmaceutical companies have also started to show an interest in radiotherapeutics, and the development of these radio-labelled drugs for larger non-orphan diseases has raised fresh investments.

IV. ETHICAL AND REGULATORY LIMITATIONS

1. Regulation and Administration

Radiopharmaceutical products are drugs that combine both the constraints of the pharmaceutical field and those of the nuclear field. Firstly, it is necessary to develop, produce, and make available to both physicians and patients a product the effectiveness and pharmaceutical and biological quality of which is guaranteed. Secondly, the production, distribution, and administration of a radioactive substance must be guaranteed, while protecting the environment and staff coming into indirect contact with it. In consequence, two distinct administrative authorities usually have the duty and power to monitor compliance with specific rules at all times – sometimes under the control of two separate ministries. This monitoring does not just apply to developers, producers, and transporters, but also to users, namely hospital physicians and radiopharmacists. In particular, these authorities are responsible for checking the suitability of the relationship between the licences they grant and the training given to staff in using radioisotopes – the latter being sometimes managed by a third administration. If the legislation on pharmaceutical products is constraining, the one on radiopharmaceuticals is even more so.

2. Side Effects and Toxicity

Each time a drug is administered – and not just in the case of radiopharmaceuticals – there potentially exists an associated danger for patients. Physicians who are aware of the limits of the products they administer must minimise this risk while pressing on with

the treatment in such a way as to promote healing. Most drugs are extremely harmful products, but are used in doses where the toxic levels are not reached. In certain circumstances, some side effects are tolerated which are in reality the visible side of these toxic effects. Chemotherapy, a treatment that is extremely aggressive for the whole organism, is unfortunately only efficient at doses that also create significant side-effects such as nausea and vomiting, hair loss, and gastric problems, and above all bone marrow toxicity. Reducing a dose in order to minimise the side effects only reduces its effectiveness, and is therefore riskier to the patient in the end. While waiting for even more specific and less traumatic chemotherapies, many palliative treatments for these side-effects have been developed. At this level of therapeutic need, the observed side-effects are accepted by physicians and tolerated by patients.

In the case of radiopharmaceuticals, the risk is doubled. Patients first suffer from a vector's toxicity equivalent to that described for pharmaceutical products, and then from the effects associated with radiotoxicity. Taking into consideration the extremely low quantities of active materials injected in patients, the toxicity of the vector plays no role – except perhaps in allergic phenomena. As a consequence, developers of new radiopharmaceuticals have the means to accelerate their research process, without dwelling too much on toxicity problems inherent to the vector. The toxic side-effects are so low that it could even be possible to use, as a base for vectors, molecules which are rejected by the pharmaceutical industry because of their high level of toxicity.

In all cases, radiotoxicity will need to be taken into consideration at the first level. Researchers are increasingly focusing on the same small group of radionuclides, the radiotoxic characteristics of which are starting to be well-established, or at least, where the doses which should not be exceeded are well-known.

As with chemotherapy, higher doses have significant consequences for the individual and also lead to modifications in blood count

– and even to bone marrow failure. On the other hand, external or metabolic radiotherapy is only rarely accompanied by side effects. At the very most, a certain level of digestive troubles has been observed, as well as a burning sensation at the injection point. Therapeutic nuclear medicine has the great advantage of displaying very limited drug-linked morbidity for patients. Hospitalisation is rarely required for diagnosis analysis; it is not linked to the imaging method, but to the treatment or monitoring of the patient.

3. Dosage and Indication Extensions

The radiopharmaceutical quantity delivered to the physician for injection is usually slightly higher than the quantity to be administered to the patient. Due to decay, the dose is much stronger upon leaving the factory or radiopharmacy – and it takes the theoretical injection time into account. The nuclear physician will have to calibrate the dose for the time of application, to ensure that the actual prescribed quantity will be fully injected into the patient. A possible dosing or handling error on the part of the radiopharmacist or physician must also be taken into consideration.

As a precautionary measure, but without any evidence to support it, children and pregnant women are normally excluded from diagnosis procedures involving radionuclides. Nevertheless, children can undergo radiotherapy in extreme situations. If it is not too late, it is preferable to offer pregnant women suffering from cancer an abortion before treatment. In fact, these questions raised by physicians remain the same whether they concern a child or a pregnant woman undergoing chemotherapy.

Legislation on annual dosage limits for injected radioactive substances does not apply to patients. It is obvious that any examination must be justified for a certain indication, as well as for the equipment used. The expected benefit must exceed the long term risk by a wide margin. It must also particularly take into consideration the possible appearance of new cancers. This is one of the reasons

why therapeutic treatments are generally only intended for patients without any other alternative.

However, limiting needless radiation remains a priority. The choice of dose delivered must remain sufficient so as not to compromise the diagnosis result or the therapy's effectiveness. As with chemotherapy, radiotherapists and nuclear physicians will work at the limits of toxicity with a concern for maximum effectiveness and minimum risk. To this end, they are ready to accept some unavoidable transient side-effects.

V. POLITICS AND LEGISLATION

Radiologists and nuclear physicians both need a certain level of autonomy in their respective sectors. Each specialist's field of competence still needs to be clearly defined, and the situation gets even more complicated when budget and funding become part of the discussion. In fact, radiologists, who have been longer established and are responsible for X-ray and Magnetic Resonance Imaging, could claim to cover the whole diagnosis sector. Nuclear physicians on the other hand, specialists in a very specific field and responsible for all the consequences of using radioactive products, consider themselves more as practitioners who evaluate the progression of a disease, rather than mere technicians responsible for a specific tool. Unfortunately, their operating budget is among the lowest in the hospital, and the number of hospitals equipped with a nuclear medicine department is also very low. A further complication is added with the arrival of metabolic radiotherapy products which could be part of the radiotherapist's field. Unfortunately, the latter – even though they are nuclear specialists – are only authorised to apply radiation from an internal or external, but sealed, source. As seen so far, given that metabolic radiotherapy only has specific applications in certain fields such as oncology or rheumatology, it is prescribed by oncologists, haematologists, or rheumatologists who sometimes consider nuclear medicine to be a service department.

A nuclear physician does not have the training nor the experience of an oncologist; an oncologist does not have any radioactive material handling knowledge; a radiotherapist is not authorised to inject a radioactive product; and a radiologist is only involved in diagnosis techniques. As a consequence, all of them must work together as a team. The hospital departments in which nuclear medicine has made the most progress are those where both nuclear physicians and oncologists manage to get on well with each other. Indeed, in this way both can find their place and be useful to one another, without attempting to manage the other's department.

A nuclear physician's annual budget is provided to cover a certain number of tests in the areas of cardiology and oncology. It would be spent within a few weeks if it also had to cover the costs of therapy products. Oncologists and haematologists have the most expensive drugs available for use in chemotherapy, and could in the future make substantial savings by replacing certain chemotherapy treatments with radiotherapy treatments – but they are not yet sufficiently trained in, or rather informed about, these techniques. A few more years are required in order to improve budget allocation at hospital level, but this will only happen if the health authorities set new rules which would be beneficial to both patients and the state budget.

On the basis of budget limitations affecting health spending and the reorganisation of departments, the only alternative for all these specialists consists of implementing real co-operation and multidisciplinary team work. Within a few years, centres specialising in metabolic radiotherapy – and enjoying very good reputations – will appear. These centres will succeed in creating an effective team for the treatment of cancers using all the new techniques, based around a unifying and charismatic manager, whether this manager is an oncologist, a radiologist, a radiotherapist, a nuclear physician, or a hospital director.

Theranostics are introducing a new game changer. The selection of positive responders to a therapy will reduce the number of

treatments, and indirectly impact the global healthcare budget. This may be compensated by higher prices for therapeutics.

VI. THE FUTURE

Since it demonstrated its real effectiveness 70 years ago, nuclear medicine – and more particularly radiopharmaceuticals – has progressed in stages. The 50s and the first half of the 60s showed the therapeutic efficacy of Iodine-131 and Phosphorus-32 used in the simple chemical form of salts. At the same time, Technetium-99m and certain derivatives made their appearance, in particular pyrophosphates allowing for the first images to be produced. During the 15 years that followed, other Technetium-99m derivatives were developed in the form of organic complexes, colloids, macro-aggregates, and salts, which produced images of specific organs and tissues. From the 80s onwards, technetium chemistry evolved in such a way that substances which could be used in the perfusion of specific tissues could help observe the functioning of certain organs – such as the heart, the brain, and the kidneys in particular. In the 90s, research turned towards targeting groups of similar cells. Through this new approach, substances concentrating in specific tissues were identified, and a certain class of cells could thus be located. Since the beginning of this century, chemists working with oncologists have been systematically suggesting to replace imaging isotopes with therapy isotopes on complex molecules in order to destroy the cells to which these molecules bind. Effectiveness of this approach has been proven, and interest in theranostics has grown. New radiotherapeutics are now reaching the market and starting to target neuroendocrine tumours and prostate cancer. We are only at the beginning of this therapeutic revolution. The first years of this century saw the market introduction of a new class of therapeutic products based on antibodies. These products are demonstrating real clinical effectiveness in the treatment of cancers. Other products

such as peptides and engineered antibodies have followed, and new molecules will appear on the market within the next years. The development of this technology, which requires specific equipment, depends on two key factors: firstly, the financial and human resources granted to this field of medicine for its development with patients, and secondly the acceptance by physicians specialising in oncology (competitive aspect), politicians (demagogy aspect), and the public (safety aspect). Finally, it is the patients themselves who are the direct beneficiaries of the technology, and they are the only driving force (such as lobbying groups) who will push for a faster development of this field in the short term.

Due to the high costs, to the limited number of approved handling centres, and above all to the lack of knowledge of this technology, metabolic radiotherapy has been confined to the role of a last-hope modality. Clinical studies in progress involving the new products were only initially intended for patients who do not respond to "standard" therapies (chemotherapy and external radiotherapy). Results achieved in recent years and the availability on the market of new and effective products filling the gaps left by chemotherapy will doubtlessly stimulate developments in this field. We are at the onset of a major change in this field, and a series of new radiotherapeutics under development will reach the market very soon. Step by step, metabolic radiotherapy will move from being solely used to treat incurable cancers and end-of-life patients to being a second-line treatment. Then, if it proves its worth, it could even replace certain chemotherapy protocols. Each stage must be demonstrated.

In oncology, the reference criterion is survival. This criterion is easy to measure when physicians limit their interest in patients who have a short life expectancy. They just need to count the patients who are still alive two or three years after the treatment, and compare this number with the control group in order to prove the treatment's effectiveness. If the studies consist of treating patients whose life expectancy is in excess of a year, they no longer have to wait for two

years; instead, they must wait at least five years before giving their verdict. In addition, these studies will always be limited to a subgroup of patients suffering from a well-defined cancer. Individualised therapy is becoming increasingly evident.

Truly effective metabolic radiotherapy drugs are only just beginning to appear on the market. They are the forerunners of products on which great hopes are based, and they will soon compete with chemotherapy products to the patient's benefit.

GLOSSARY

Absorbed dose: quantity of energy transferred to a substance per kilogram during absorption of radiation, expressed in grays.

Acquisition: recording of all the radiation accumulated over the course of a predetermined period of time in order to obtain an image.

Activity (radiological): value representing the number of disintegrations per second from a radioactive source, expressed in becquerels.

Affinity: property of a substance to bind to a receptor; it is a measurement of the strength of the binding.

ALARA: As Low As Reasonably Achievable. Radiation protection policy related to the management of staff working in an ionising radiation environment. The acronym ALARP (As Low As Reasonably Practicable) is slowly replacing ALARA.

Alpha (α) (alpha radiation): a particle emitted by a radioisotope and formed from a nucleus of helium containing two protons and two neutrons with potential therapeutic uses due to its strong ionising power.

Auger (electrons): low energy electrons emitted from the surface of an atom, following an interaction with an external incident electron or photon, but endowed with ionising power at a short distance and therefore usable in therapy.

Becquerel (Bq): unit of radioactivity equal to one disintegration per second. The becquerel replaces the former curie unit, one curie being the equivalent of 37 billions becquerels.

Beta-minus (β^-) (beta-minus radiation): a particle emitted by a radioisotope and formed from a negatively charged electron, usable in therapy due to its ionizing (destructive) potential.

Beta-plus (β^+) (beta-plus radiation): a particle emitted by a radioisotope and formed from a positively charged electron (positron), an unstable antielectron, which upon meeting a negatively charged electron is annihilated to emit two gamma photons, themselves moving in exactly opposite directions, and therefore usable in imaging. This radiation could possibly be used in therapy.

Biological half-life: time period at the end of which a cell or tissue has eliminated half the quantity of a molecule present by a biological metabolism mechanism followed by excretion.

Brachytherapy: method of internal irradiation by the temporary or permanent introduction of radioactive implants. Examples: radioactive seeds marked with Iodine-125 in prostate tumours, Iridium-192 wires in breast tumours, Phosphorus-32 patches (also called *Internal Radiotherapy* or formerly, Curietherapy).

Calibration: used in the expression "at calibration", meaning at the time at which the product will be used. The dose shipped has a higher activity when leaving the manufacturing plant and guarantees the announced activity at the time of use, taking partial decay during transportation into account.

Cold kit: non-radioactive precursor of a radiopharmaceutical containing all the elements that enable this medication to be reconstituted instantaneously, simply by adding a radionuclide solution.

Computerized Tomography (CT): cross-sectional imaging allowing three-dimensional reconstruction.

Contamination: physical contact leaving a deposit of radioactive material on a surface, matter or person. The contaminated person is

irradiated as long as the active matter has not been eliminated, or the radioactivity has not fully decayed naturally.

CT: abbreviation of Computerized Tomography (if not specified these are X-rays).

Curie (Ci): one curie corresponds to the radioactivity emitted by one gram of pure Radium-226, one of the first natural radioactive materials available and isolated at the beginning of the last century. In principle, this unit should no longer be used because it was replaced by the becquerel *(see entry for this word)* in the 80s.

Curietherapy: *see Internal radiotherapy.*

Decay: reduction in the level of radioactivity over the course of time.

Dosimetry: the study and measurement of absorbed radiation.

Effective dose: the equivalent dose corrected by the weighting coefficient relating to the irradiated tissue (0.05 for the thyroid, 1 for the whole body) expressed in sieverts.

Effective half-life: radioactive half-life corrected by the biological half-life. With it, the practitioner can estimate how long a radioactive substance that has been ingested or injected will take before generating an effect on the organism (or a certain type of cell or tissue).

EMA: European Medicines Evaluation Agency, European Health Authority, centralised in London, formerly EMEA (European Medicines Evaluation Agency).

Equivalent dose or Dose equivalent: absorbed dose corrected by a weighting coefficient relating to the radiation (1 for X, beta and gamma rays, 20 for alpha rays), expressed in sieverts. This is a value used in radiation protection to take account of the difference in biological effect of the various radiation types.

External radiotherapy: method of therapy by irradiation using a source external to the patient (cobalt therapy). Domain of the radiotherapist.

FDA: Food and Drug Administration, American Health Authority.

FDG (Fludeoxyglucose): substance labelled with Fluorine-18, most frequent tracer used for diagnosis based on the Positron Emission

Tomography method. It is a radio-labelled glucose analogue that allows glucose-consuming cells, such as tumour cells, to be displayed.

Free radical: an extremely reactive chemical entity which contains a redundant electron and which is at the origin of later chemical transformations.

Galenic: study of the method of administering a medication.

Gamma (γ): radiation of a shorter wavelength than X-rays emitted by certain radionuclides and with very high energy, usable for diagnosis imaging.

Generator: tool for the production of a radioisotope by the decay of a parent radionuclide from which it is regularly separated by a physical means (column filtration, extraction). A generator is said to be "milked" to obtain the solution of the bulk daughter radionuclide.

GMP - Good Manufacturing Practice: guidances to follow (usually general principles to observe) in order to conform to the agencies' recommendations for obtaining the authorization and licensing for manufacture and sale of drugs and active pharmaceutical products. GMP ensures quality. The first mention of GMP dates back to 1990.

Gray (Gy): unit of absorbed dose corresponding to one joule per kilogram. The former unit of absorbed dose is the rad, with one gray equalling 100 rads.

Half-life: radioactive half-life, *see Radioactive half-life.* The term biological half-life is also used, which corresponds to the time at the end of which half the quantity of a substance has disappeared or has been eliminated from a cell by a biological process.

Internal radiotherapy: method of therapy by irradiation using a sealed radioactive source inserted into a natural cavity or implanted, temporarily or permanently, into the tissues. Synonym for *Curietherapy* and *Brachytherapy.* Domain of the radiotherapist.

Intracavity radiation: the emission of rays from a source placed inside a cavity: uterus, throat.

Intraoperative radiation: irradiation during a surgical operation.

Ionising (radiation): electromagnetic or corpuscular radiation capable of producing ions (positively or negatively charged atoms or molecules) directly or indirectly during its passage through the matter. This transformation of the molecules is considered as being destructive and induces a biological change. X and γ rays are considered as weak ionizers compared with β^- and above all with α.

Irradiation: exposure to radiation without physical contact with the radioactive material, not to be confused with contamination in which there is a transfer of radioactive material. Once outside the radioactive field, the person is no longer exposed to the effects of the radiation.

Isotope: all the atoms, the nuclei of which have the same number of protons, form a chemical element. Natural elements amount 97, to which 21 artificial elements must be added. When a given number of protons are associated in an atom with different numbers of neutrons, they represent variant chemical elements called isotopes. In most cases, only a few forms are stable; the other unstable forms are called radioisotopes or radionuclides. Of the 118 elements currently known, 36 exist only in an unstable, that is to say radioactive, form. This is the case for uranium, plutonium, and radium. There are so far more than 3,500 identified radionuclides, among which about 200 could play a role in nuclear medicine.

Label: an entity (simple or complex) which, due to its radiation or its colour, can be monitored in a complex biological system.

Labelling: method of chemical fixation of a radioisotope on a non-radioactive molecule.

Ligand: small molecule that forms a complex with a biomolecule such as a receptor (one says it binds to the biomolecule) to serve a biological purpose. Ligands serve as transporters of the radioactive charge, and are in this case called vectors.

Metabolic radiotherapy: method of therapy by selective irradiation of a target zone by a molecule participating in the metabolism and labelled with a radioisotope, injected into the patient. Domain of the nuclear physician.

MRI: Magnetic Resonance Imaging, another name for Medical Nuclear Magnetic Resonance.

Neutron: a neutral elementary particle (with no electrical charge), a constituent of the nucleus of the atom together with the proton.

Neutron therapy: external radiotherapy using a neutron beam.

Nocebo (effect): an undesirable effect of a treatment not linked to an active substance, but essentially to an unconscious non-controlled perception on the part of the patient. Opposite of the placebo effect.

Nuclide: atomic nucleus.

Oncology (or cancerology): medical science covering the field of the prevention, detection and treatment of cancers.

PET: Positron Emission Tomography.

Placebo: substance presented in the form of a medication, which contains no active element and which may still have a therapeutic effect on the patient. By extension, the placebo effect stands for any positive effect on the evolution of an illness not linked to an active substance. The opposite, a negative effect, is called a nocebo effect.

Positron: *see Beta-plus.*

Posology: dosage and procedures for administering a medicine.

Proton: a positively charged elementary particle, constituting the nucleus of the atom together with the neutron.

Proton therapy: method of external radiotherapy using a proton beam.

Rad: *see Gray.*

Radiation: a beam of invisible particles or waves emitted by a source. Also, the process of transmission of energy in corpuscular (α, β, etc. particles, etc.) or electromagnetic form (visible light, ultraviolet, infrared, X, γ, etc.).

Radioactive half-life: time at the end of which half the atoms initially present in a radioactive element have disappeared through spontaneous transformation. This period (half-life) varies from one radionuclide to another, but is a precise physical constant for a given radioisotope, and is neither influenced by temperature nor pressure.

Radioactivity: property of certain radionuclides which emit particles spontaneously (electrons, protons, neutrons, nuclei) and/or γ or X-rays.

Radiochemical: a radioactive substance, not intended for human use.

Radiochemist: a chemist specialising in the manufacture of radioactive substances, therefore in the nuclear medicine field, a specialist in the development of labelling, and in the nuclear physics field, a specialist in the chemistry of radionuclides.

Radiochemistry: chemistry of substances incorporating a radioactive element.

Radioelement: an element where all the isotopes are radioactive, like for example those of the Plutonium or Uranium groups (term often used wrongly in the place of radionuclide or radioisotope).

Radioisotope: An unstable isotope that decays over the course of time, emitting radiation *(see radionuclide)*.

Radiologist: specialist in X-ray imaging.

Radionuclide: radioactive atomic nucleus. Two radionuclides compared with each other are called radioisotopes if they belong to the same family of atoms (e.g. the radioisotopes of iodine such as Iodine-123, 124 or 131), and radionuclides in the other cases. The word in the plural "radioisotopes" is frequently used wrongly to designate all radionuclides.

Radiopharmaceutical: radioactive medication intended for diagnosis or therapy in the field of nuclear medicine.

Radiopharmacist: a hospital pharmacist specialising in the labelling and handling of radiopharmaceutical preparations intended for administration to a patient.

Radiopharmacy: a laboratory, principally located in a hospital, equipped to handle radioactive substances for the injection into patients.

Radiophysician: physician specialising in the handling and production of radionuclides.

Radiotherapist: physician specialising in treatment by external radiotherapy. In case the radioactive substance has to be injected into the patient, responsibility is entrusted to the nuclear physician.

Radiotherapy: method of therapy (treatment of a disease) based on the use of radiation, of whatever sort (X-rays, alpha, beta, neutrons, etc.).

Rem: *see Sievert.*

Scanner: an imaging tool using X- or gamma rays that provide virtual sectioning (scans) of the area being analysed.

Scintigraphy: method of imaging based on recording γ radiation emitted by a substance injected into the patient and which concentrates in a particular organ or tissue (heart, thyroid, bones, etc.).

Sealed source: a radioactive substance placed in a sealed container, irradiating but not contaminating. The implants used in internal radiotherapy are sealed sources.

Side effects or **undesirable effects:** disturbance to the state of health of any sort not linked to the principle illness, but more often to the treatment itself. For example: headaches, gastric trouble, nausea and vomiting, hair loss, changes in blood count, as a cause of, or parallel to, chemotherapy.

Sievert (Sv): unit of equivalent dose, corresponding to a corrected dose of the ionising effect of the radiation (for X, β and γ radiation, 1 Sv = 1 Gy). Previously the rem was used, with one sievert being equivalent to 100 rems.

Source: origin of radiation. By extension, the radioactive substance itself.

Specific activity: value corresponding to the relationship between the activity of the radionuclide and the total mass of the element present. When the radioisotope is present in its pure form, even in an extremely dilute solution, we talk about a **carrier free** radioisotope solution. It is expressed in becquerels per mass unit.

Specific concentration: value that determines the degree of radioactive substance per volume unit. It is expressed in becquerels per volume unit.

Specific – specificity: describes molecules that only target a single type of cell or receptor.

SPECT: Single Photon Emission Computed Tomography.

Targeted or vectorised radiotherapy: a more general term including metabolic radiotherapy. This nuclear medicine technique consists of treating a specific tissue of the organism with ionising radiation, itself originating from the concentration of a substance which participates in a biological mechanism (the vector), and to which a suitable radionuclide is grafted.

Theranostics: a form of diagnostic testing employed for selecting targeted therapy. Also, a combination of a diagnostic agent with a specific therapeutic protocol or drug.

Tomography: radiography providing a clear image of a single cross- section.

Tracer: radiolabelled substance used in diagnostic procedures.

US: ultrasound.

Vector: chemical substance which has the property of being recognized by certain macromolecules present in tissue (receptor, enzyme, etc.) and on which another toxic or radioactive substance is grafted, for therapeutic or diagnosis purposes.

X-rays: invisible, short wave, light radiation, produced by a radioactive substance and capable of crossing material.

FOR FURTHER READING

In the world, very few nuclear medicine books are written in a language that can be understood by almost everyone, and none of the older published ones have been recently updated. Actually, this is the aim of this book. The following is a reference list of books generally intended for physicians. They are a good source of complementary information for specific topics, but the required scientific knowledge is of a high level.

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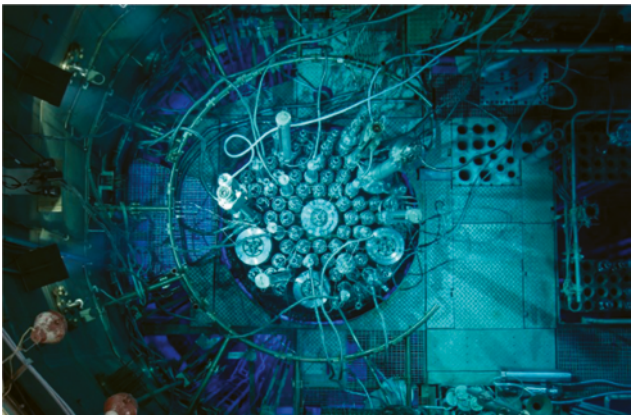
The most up-to-date information about radiodiagnostics and radiotherapeutics for the general public, as well as the progress made in nuclear medicine, can be found on the Oncidium Foundation website under www.oncidium-life.org.

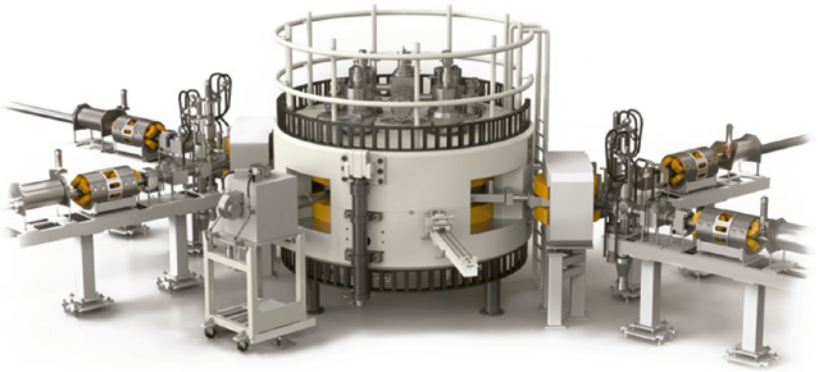
The Oncidium Foundation is devoted to the promotion, clinical development, and distribution of radiotherapeutics in the treatment of cancer all over the world. The Foundation aims at broadening the knowledge of nuclear medicine for therapy by supporting all initiatives that will improve access, even in remote places.



1.

Heart of the BR2 reactor in Mol, Belgium in which radionuclides, such as Molybdenum-99 or Lutetium-177, are produced by neutron irradiation. The process takes several days, and the individual targets need to be processed in an industrial hot cell that can handle several hundredths of curies. The extracted raw material is then shipped to dedicated pharmaceutical industrial centres, where it can be further purified and transformed into either a ready-to-use drug or an active material part of a generator.

Courtesy SCK-CEN, Mol, Belgium



2.

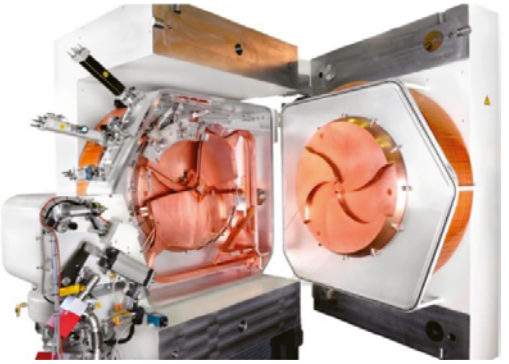
Large-size cyclotrons (example here is 70 MeV) are used for the production of radionuclides, mainly for SPECT imaging (such as Thallium-201 or Iodine-123), for precursors in generators (such as Strontium-82 or Germanium-68), or radionuclides for therapy (Astatine-211). The cyclotron itself is about 3 m high, and this example shows four exits directed towards four different targets, allowing the production of several different radionuclides. This tool must be operated in a vault; due to the high energy, concrete walls can reach up to 4 m in thickness.

Courtesy: IBA Louvain-la-Neuve, Belgium

3.

Middle-size cyclotron for the production of Fluorine-18 for example (here 18 MeV). These tools are about 3x3 m in size, and 2 m in height; they need to be operated in a vault of concrete, with walls of about 1.5 m in thickness. Once the irradiation process is complete (a couple of hours), the target or the target content is transferred to a hot cell outside of this room, where it is processed and transformed into a pure radionuclide solution.

Courtesy IBA, Louvain-la-Neuve, Belgium



4.

View of an open cyclotron (illustrated here in a model with a vertical magnet) showing the four dees (copper parts) allowing the acceleration of the charged particles (protons, deutons, or alpha particles) in a circular path before hitting the targets shown top left.

Courtesy GE Healthcare

5.

Synthesizer for the production of radiolabeled drugs. Within a hot cell and behind leaded thick walls, larger amounts of radiolabeled compounds such as ^{18}F-FDG are produced automatically with such devices. This guarantees the full protection of the operator, and the reproducibility of the radiolabeled drug manufacturing. At the end of the process, the bulk solution of the radiolabeled drug needs to be split into individual doses in a dispensing unit. Samples are taken for controlling the quality of the final product before shipment and injection to the patient.

Courtesy IBA Louvain-la-Neuve, Belgium

6.

Dedicated hot cell used in a hospital radiopharmacy to handle radiopharmaceuticals locally, e.g. to prepare mono-doses in syringes from vials containing bulk solutions, or to produce radiotracers, usually from cold kits and radionuclides issued from a generator (^{99m}Tc or ^{68}Ga).

Courtesy LemerPax Nantes, France.

7.

The radiotracer is injected in the patient who, after some rest, is scanned with a special camera, either PET or SPECT, depending on the radio-emitter used in the procedure. The picture shows a patient screened in a PET/CT camera after injection of ^{18}F-FDG, while the operator monitors the whole image acquisition process.

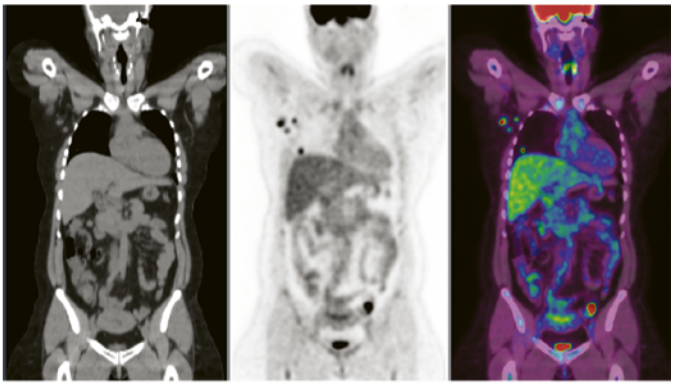
Courtesy SWAN Isotopen, Bern, Switzerland

8.

Hybrid imaging: PET/CT camera
To a neophyte, nuclear medicine equipment does not seem to differ much from MRI equipment or CT tools. Hybrid imaging tools combine two of these modalities in a single equipment, and nowadays three hybrid systems are available: SPECT/CT, PET/CT, and less common because costlier, PET/MR.

Courtesy Philips Healthcare

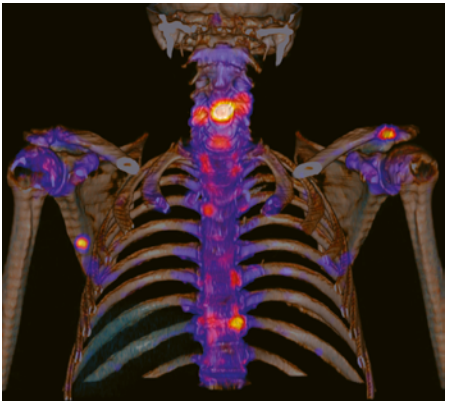
9.



PET/CT Hybrid imaging: the CT (X-ray) imaging provides a detailed anatomical view of the body (on the left). After injection of the tracer, a Positron Emission Tomography (PET) image is obtained (middle) and the combination of both (fusion) allows to precisely identify and localize the prostate cancer metastases in this patient (large red spot on the bottom right, and several small spots under the arm on the top left). The red spot at the bottom of the image in the middle is a simple accumulation of radioactive substance in the bladder. On the computer screen, the physician has access to a three-dimensional image, and can rotate and focus on these images as required.

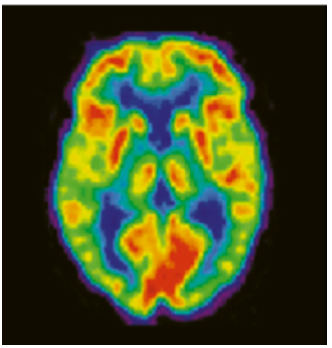
Courtesy Philips Healthcare

10.



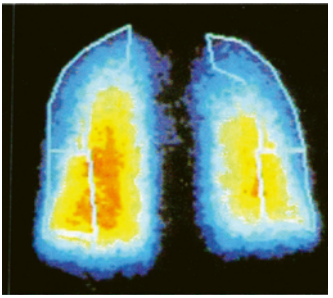
SPECT/CT hybrid image: this image clearly shows the bone metastases of a prostate cancer patient using a technetium-99m labeled tracer (^{99m}Tc-DPD) with the hybrid technology CT (X-rays) and Single Photon Emission Computed Tomography (SPECT). The 3D fusion image that can be rotated and zoomed can precisely define the extent of the disease.

Courtesy University of Erlangen, Siemens Healthineers



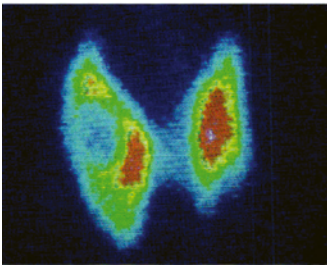
11. Positron emission Tomography (PET) is ideal for studying brain behaviour. As a consequence of the rapid distribution of the Carbon-11 or Fluorine-18 labelled molecules in the brain and the short half-lives of these radionuclides, it is possible to observe how flawed brain cells compare with healthy ones, as well as to study how the activated brain areas respond to specific stimuli (think, look, move, etc.). The most recent fluorinated tracers to reach the market allow for a very early diagnosis of neurodegenerative diseases, several years before clinical onset. This image shows a ^{18}F-FDG PET scan of a healthy subject's brain.

Courtesy CEA, Orsay France (L. Medard)



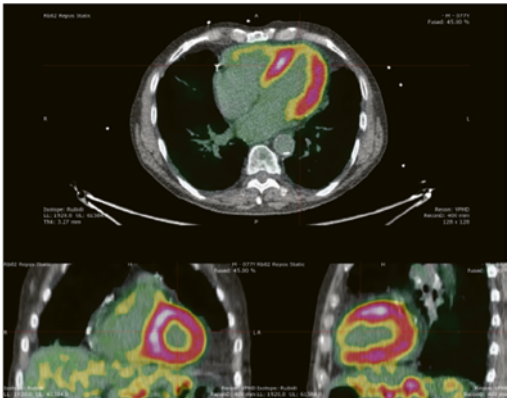
12. Pulmonary ventilation imaging is obtained by inhalation of a radioactive gas. The higher the pulmonary capacity is, the higher the radioactive area will be. Colours of varying intensities indicate the concentration level of the radioactive substance. Obviously, the image showing a badly ventilated lung (right) is incomplete compared to that of a normal lung (left).

Courtesy IBA Molecular/CIS bio international, Saclay, France



13. Injections of Iodine-131 show a very clear and specific image of the thyroid, as this organ absorbs iodine very easily and even selectively. The slightly emitting area located on the left side of the image (right thyroid lobe) clearly indicates the presence of an isolated and well-delimited cold nodule. The subsequent ultrasound analysis will help define whether the nodule is a solid benign tumour (cellular excrescence that prevents the organ from functioning properly) or a cyst. In the case of a hot or hyperbinding nodule, Iodine-131 (gamma and beta-minus emitter) can be used at low doses for imaging, and at higher doses for therapy purposes, via the destruction of the cells on which it binds. Iodine-131 will be as efficient in destroying thyroid cancer metastases.

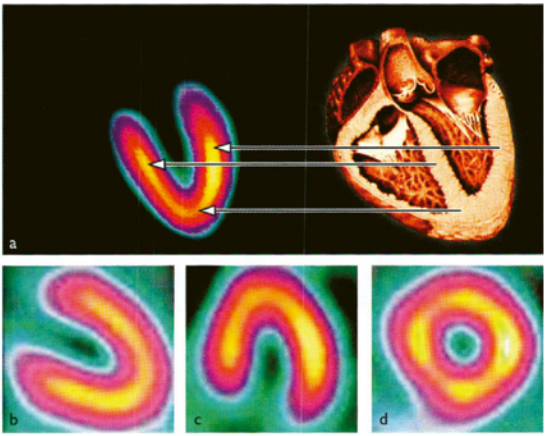
Courtesy IBA Molecular/CIS bio international, Saclay, France



14.

PET cardiac imaging using Rubidium-82 as a tracer. The three images clearly show the shape of the cardiac muscle from three different angles (top, front, and side). Defects identified in the overall shape of the muscle heart are indicative of ischemia or necrosis.

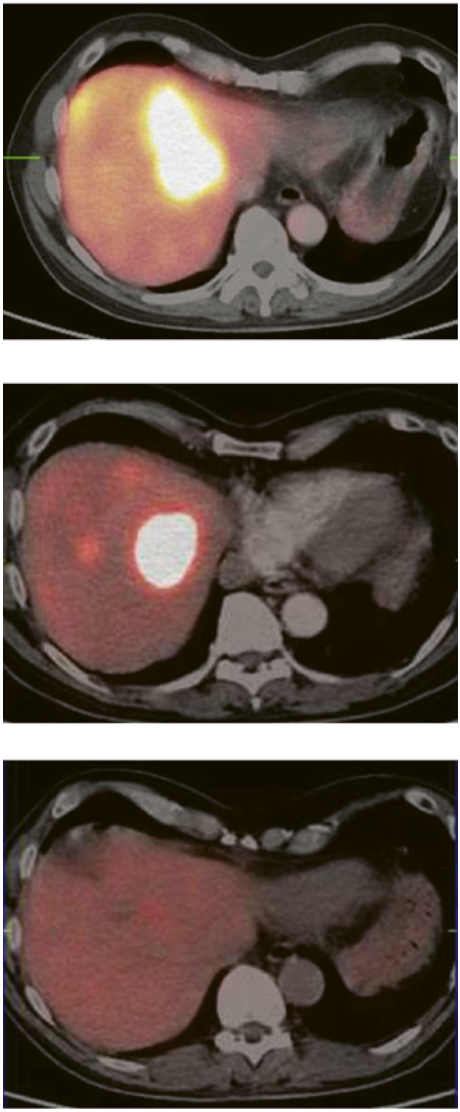
Courtesy Keosys Nantes, France



15.

(a) Cardiac image obtained after injection of Technetium-99m tetrofosmin. The radioactive substance is integrated into the active healthy cells. The cells' incorporation level is directly linked to the rate of radioactivity, which is represented by a colour scale depending on the intensity level. One can therefore clearly superimpose the muscular part of the heart that will show a U-shape in a section scanned from the front (b) or from the side (c), and a doughnut shape (d) if seen from the top. Any reduction in size of this area, any missing colours indicate an ischaemic area. If the image of this area does not resume to a normal colour set following a stress test (bicycle or treadmill), one can consider that this area corresponds to a necrosis. Medical treatment will be adapted accordingly.

Courtesy GE Healthcare



16.

Efficacy of radiotherapeutics. From top to bottom: (a) large liver metastasis in a patient with Neuroendocrine tumor (pancreas cancer) before treatment – at this stage, life expectancy was about 6 months; (b) same patient one year after treatment with Yttrium-90 labeled somatostatin analogue; (c) liver image taken 3 years after treatment with the Lutetium-177 labeled somatostatin analogue. Images were obtained with the Gallium-68 somatostatin analogue.

Courtesy Zentralklinik Bad Berka, Germany (Prof R. Baum)