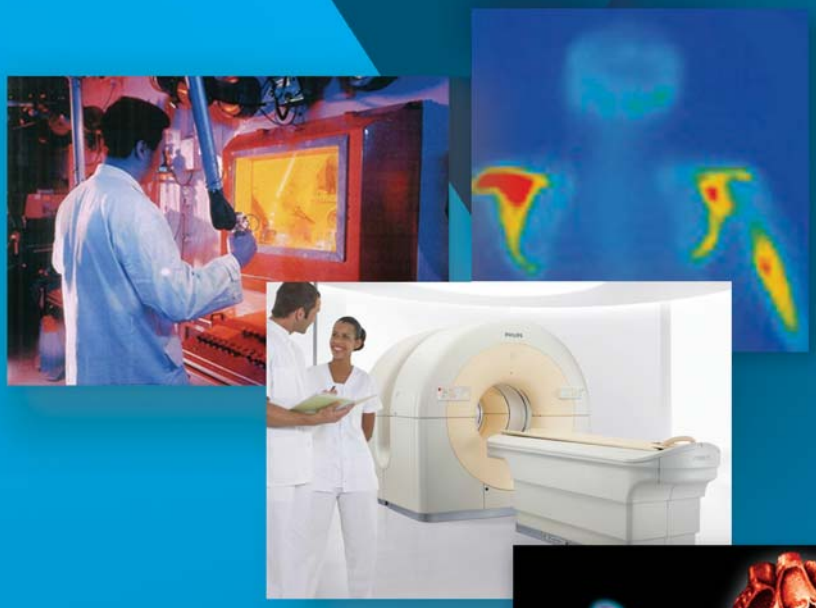
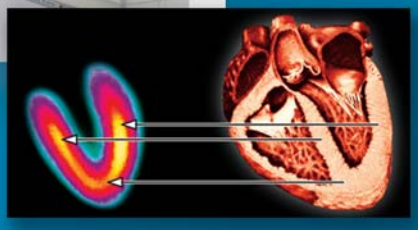
Nuclear Medicine

Radioactivity for Diagnosis and Therapy





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EDP SCIENCES

Nuclear Medicine

Radioactivity for Diagnosis and Therapy

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In memory of my father

This work is dedicated to all the anonymous persons who are directly or indirectly involved in the preparation, the handling and the application of radiopharmaceutical drugs. They are technicians, cyclotronists, engineers, pharmacists, biologists, clinicians, scientists, archivists, salesmen, specialists of radioprotection, safety, quality, logistics, environment, regulatory affairs, maintenance, etc., and without their precious contribution nuclear physicians 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 little known, extremely complex and particularly efficient drugs.

Preface

Richard Zimmermann firmly believes in the huge possibilities offered by nuclear medicine. At a time when the public hears about Positron Emission Tomography, at a time when this new technology seems to give a second breath to our speciality, it was clever to propose a didactic work allowing to better understand nuclear medicine. Richard Zimmermann provides the reader with a book that is complete, describing with great accuracy yet in an attractive and comprehensive style all the technical, methodological and pharmaceutical aspects of nuclear medicine, covering also its diagnostic and therapeutic applications. This book proves to be a valuable information source for our young students as well as for hospital intern specialists. Others will find it very useful when promoting this too little known discipline. This work must be made available in all our university libraries, and it must be read by all those in charge of health politics.

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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 therapeutics. In both cases, a substance containing a radioactive isotope or **radionuclide** (one speaks about a labelled substance) is administered to a patient. It goes straight towards a biological tissue or organ after having selectively searched for it. 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 it is grafted. The emitted radioactivity will then be used either to locate the radionuclide (diagnosis) or to initiate the deterioration of surrounding 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. The selection of the radionuclide, based on the nature of the emitted radiation, its physical properties, *i.e.* energy and half-life, and its chemical properties, will define the final purpose of this molecule, called a **radiopharmaceutical**. The diagnosis imaging technology, also called scintigraphy, is obtained with substances labelled with γ-emitter isotopes. The development of the imaging acquisition technology associated with powerful information technology software resulted in the development of the tomography technology,

which involves cross sections and tri-dimensional images. Some radioactive elements can be used for therapeutic purposes thanks to their physico-chemical properties, based on the destructive effect of the ionising radiation emitted by the labelled substance. The use of these vectors in association with therapy radionuclides, essentially β^- or α emitters, is called **vectorised** or **metabolic radiotherapy**.

The use of radionuclides as an external source of radioactivity, of temporary radioactive implants for therapy purposes or of particle beam generators (neutrontherapy and protontherapy, which are both external therapies) is controlled by radiotherapists. Hence, it does little or not concern nuclear physicians. The same applies to **brachytherapy,** or **curietherapy** as it is known in some countries, a technology that is devoted to the use of permanent or temporary radioactive implants. These areas will however 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.

CHAPTER I

Nuclear Medicine, what for?

After about fifty years of practice and experience, nuclear medicine reached a turning point. 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, and more particularly oncologists, haematologists and neurologists.

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, using a vocabulary that is as accessible as possible, to a public that is usually not even aware that this discipline does exist 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. Physicians usually think of using metabolic radiotherapy only after chemotherapy and external radiotherapy protocols repeatedly failed. One forgets much too quickly that Iodine 131 is almost always used in thyroid cancer treatment. For the past fifty years more than 90% of all thyroid cancers have been successfully treated, and definitely cured, thanks to this nuclear medicine

method. However, one has to admit that, so far, this therapeutic success was the only one recorded following the use of this technology until very recently, by the end of the 90's.

Until then, the role of nuclear medicine was essentially limited to being a support for diagnosis, via every type of scintigraphy method developed to this day.

In this introductory chapter, we will see how patients can benefit from the knowledge acquired in nuclear medicine during the past half century, and learn about the revolutionary aspect of these new techniques and medicinal products; then, we will take a look at all the opportunities brought by this technology when it is associated to other innovative medical modalities. All these aspects will be developed in detail further in this book.

What do we call Cancer?

All living beings originate from a single cell which divided, grew and continued to multiply while it underwent differentiation, in order to form the specific cells of the 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 do not expand anymore, therefore the production of new cells concentrates on specific growth mechanisms as for hair or blood, and also as part of repair mechanisms such as skin regeneration or wound self-repair. As the lifespan of a cell is limited, its renewal is also necessary.

Taking into account the impressive number of cells which are required to build a complete body, the process regularly deviates, giving birth to cells with an unexpected structure. Also, cells are continually subject to external stress, 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, it sometimes happens that these new entities find a more hospitable, or in any case less hostile, terrain in which they can reproduce identically. When these new types of cells are not rejected by the organism, they create a new tissue that is called a tumour.

Tumours may either be benign or malignant. Benign tumours are not cancers, because they do not propagate themselves. They are easily removed without 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. To the detriment of healthy tissue, they divide, spread and travel along the blood or lymphatic system, re-implanting themselves some distance away. The new colony formed is called a metastasis, but in fact it has the same properties as the original tumoral cells. In turn, these metastases colonise other tissues, causing the disease to spread further again.

Each tumoral 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 tumour has been removed. It follows that one would not say of a person being treated for lung cancer and presenting with metastases of the liver, that they are suffering from liver cancer, but rather from a lung cancer that has spread. This person will be treated for lung cancer, a therapeutic protocol that greatly differs from liver cancer treatment.

Lymphomas and leukaemias 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 the production of normal blood cells. They are sometimes called liquid cancers in order to be distinguished from solid tumour cancers.

I. The Case of Thyroid Cancer

Iodine 131 plays a key role and so we will start with it. The earliest imaging trials, followed by the first therapeutic treatments of hyperthyroid disease with injected radioactivity, began in 1942. In 1946 it was demonstrated that not only did thyroid tumours disappear following Iodine 131 treatment, but also all metastases, thus proving the power of this technique. This incontestable efficacy is

linked to the fact that thyroid tissue is the only tissue capable of absorbing iodine. This fixation includes also the metastases, as these tissues are originating from the thyroid cells. Today, this method remains essential for the diagnosis of thyroid diseases as well as for their treatment (*see below Chapter VI, Section I*). Unfortunately it remains the unique example of human tissue fixing a radionuclide in such a specific manner, and so therapeutic nuclear medicine remains unsatisfied with this unique but major success.

Nevertheless, iodine having demonstrated some physico-chemical advantages, it remained for a long time a privileged tool for nuclear medicine. On this basis, several other radioisotopes were used for the labelling of molecules for diagnosis purposes.

II. The Diagnosis Aspect

Nuclear medicine imaging is first of all a functional imaging tool: it allows to check if a tissue or an organ works, *i.e.* is alive. Contrarily to all other imaging modalities, nuclear medicine is the only one able to prove brain death for example. Magnetic Resonance Imaging (MRI), X-rays (X) or Ultrasound (US) are unable to make the difference between dead and living tissues, and will only provide a nice three-dimensional image of the brain. It is obvious that this imaging technology is not used in this extreme case as an electroencephalogram (EEG) will provide the same information in a more simple 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 IV*). Therefore almost every organ can be visualised, and tracers are now available for nearly all tissues (bone, liver, kidney, heart, lung, gastro-oesophageal tract, etc.), and fluids (blood, cerebro-spinal liquid, urinary excretion tract, etc.)

The discovery of the utility of Thallium 201 in heart imaging, followed by that of several Technetium 99m derivatives and linked with the progress of the image acquisition technology, made this an

essential cardiology tool. Nowadays, cardiology care units very frequently resort to nuclear medicine, and are its main users: almost all persons affected from an infarct undergo scintigraphy. These tools give an accurate cardiac pump function check.

Actually, the word scintigraphy stands for all of these two-dimensional imaging techniques (*Chapter IV, 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, evolved in such a way that today three-dimensional imaging acquisition is possible. However, the amount of data to be analysed having simultaneously increased, medical applications had to wait until the end of the 90's, *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 power.

The main pathologies that have benefited from these imaging methods are:

– imaging of the lung with determination of the zones that can be reached by the inhaled air, and in parallel by the blood 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;

– 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.

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

In parallel to computer development, a new technology, the Positron Emission Tomography (PET), was introduced first in North America, and then in Europe. By the end of the 90's, 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 was slower 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. Today, in 2006, a few other countries (*e.g.* Great Britain, Canada) are in a decision-making process concerning investment, but are still in a waiting phase and therefore remain under-equipped. North Africa and South America are slowly implementing the installation of cameras. PET imaging technology can only be made available in a country when manufacturing sites for the powerful diagnostic drug fludeoxyglucose (or FDG) are also made available there (*Chapter V*). 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 non-experts can interpret the images themselves. This is not true however, as false negative as well as false-positive results do exist also, but the image remains reassuring for the physician himself.

PET technology, together with its FDG tracer, is recognised as being an extremely useful diagnosis modality for evaluating tumours: 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 surgery can also be evaluated. Benign tumours can often be differentiated from malignant ones in the absence of any response. This modality could be used to evaluate breast cancer, but other available techniques can provide equivalent information at lower cost. In the latter case, FDG remains an interesting tool to estimate the disease's level of extension, and even to monitor patients at risk of relapsing. However, this technique is less interesting for the diagnosis of renal or prostate cancers, for which more efficient imaging technologies are available.

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 V, Section V*). Important efforts have been made by clinicians to demonstrate that the not yet approved indications are valid at the level of a larger population and 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 associated computer science with PET, thus resulting in the development of mixed tools. PET/CT cameras, which combine a three-dimensional PET detection system with an 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, hence improving its removal.

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 is only rarely used for these indications.

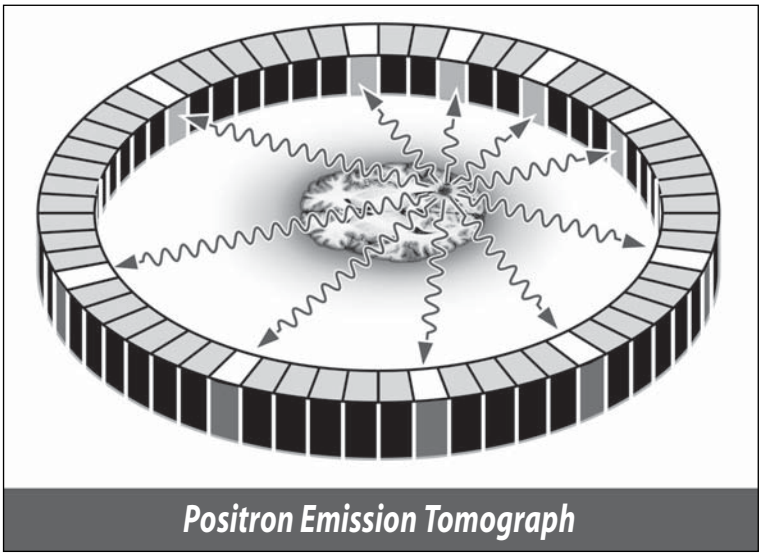

Figure 1. The annihilation of positrons colliding with electrons results in the emission of gamma photons. Those rays are taken into account by detectors placed on a level plane; this allows the acquisition of a section image of the radioactivity source (the scheme shows the section of a brain with a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

On the other hand, PET is a highly valuable tool for brain function study, and the development of new positron emitter labelled tracers, others than FDG and specific to neurological mechanisms, will probably result in improved diagnosis accuracy for neurodegenerative diseases such as Alzheimer's, Parkinson's or Huntington's diseases. The development, in parallel, of MRI technology becomes a necessity for patients affected from these diseases.

On the neurology side, a few new substances have already been marketed, but they are only used in very difficult cases. As of today, all of these diagnosis drugs are based on the SPECT technology involving gamma emitters. In fact, a whole new research field opened up 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).

1 Cancer Therapy

Beta-minus, beta-plus and alpha rays induce cellular destruction that can be turned to our advantage to destroy unwanted cells. On the contrary, radioactivity cannot be of any help concerning 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 in a patient a radioactive substance that will be integrated in the cells to be destroyed by radiations (*Chapter VI*). Iodine 131, which is described in the introduction as being useful in thyroid cancer therapy, is probably the best example of this process. In recent years, new molecules 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 resisting to classical therapies (*Chapter VI, Section III*). The treatments for less common tumoral pathologies (pheochromocytomes, neuroblastomes, polycythaemie, thrombocythaemie, 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 specificity. 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 (*Chapter VI, Section II*).

Today, these therapies are either restricted to patients in classical therapeutic failure mode, or to very limited and well identified subgroups of patients. Metabolic radiotherapy still needs to demonstrate its efficiency on a larger scale and in first line. In this regard, clinical trials are currently underway and already show encouraging results.

Other new molecules also undergoing clinical trials will become available in hospitals during the few next years, particularly for the therapy of lung or colon cancers, lymphoma, myeloma and leukaemia.

Great progress was also made in surgery techniques, breast cancer benefiting from the most innovating and effective one, the sentinel lymph node detection (*Chapter IV, Section III*). If this technique was implemented for all breast cancer patients, it should result in a dramatic decrease of cancer recurrence. Moreover, this technique is a lot less traumatic than the surgical lymphatic system ablation which is the current procedure. This technique could also be adapted to melanoma therapy as well.

Treating Cancers

Today, several cancer treatment methods are available to physicians, and they are becoming increasingly effective. 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 its development stage has been correctly evaluated.

It is important, for the well-being of patients, that they should know which therapy will be applied to them, and what it involves. It is even more important that they should be warned of potential side effects, in order to anticipate and, when possible, alleviate them. If the slightest doubt persists, 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 fairly numerous, demonstrating the complexity of care, but also the lack of a universal treatment. Let's take a quick look at the current available treatments.