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Medical A pplication of Nuclear Science: Nuclear Medicine and Production of Radiopharmaceuticals

By *Louis CORNET, CIS bio international*

I - INTRODUCTION

The Radioactivity, born with the world, is today essential in biology and in medicine.

Since 50 years, the Radioactivity has been involved in almost all progresses in these fields.

At the present time, the three main areas in medical application are:

- In-Vivo application for diagnostics or therapy (use of radiopharmaceutical products),
- Radiotherapy (use of radioactive sources or accelerated particules),
- In-Vitro application diagnosis, measurement of tumor markers.

II - HIGH LIGHTS

In the brief resumé hereafter:

Some dates ...

1896	Henri Becquerel detects the natural radioactivity
1898	Pierre and Marie Curie discover the Polonium and the Radium
1934	Frédéric and Irène Joliot discover the artificial radioactivity
1939	First leukaemia treatment with ^{32}P
1941	Two isotopes are produced for the medical use: ^{24}Na and ^{42}K
1951	Birth of the scintigraphy
1952	First French scintigraph at Curies Institution
1958	Founding of Frédéric Joliot Hospital (ORSAY) Nuclear Medicine department of the CEA
1959	First radioimmunoassay
Sixties	Sterile generator ^{99}Mo - ^{99m}Tc
Seventies	Development of Cyclotron products - Start of the tomography
Eighties-Nineties	Use of monoclonal antibodies labelled with Isotopes ^{131}I - ^{111}In - ^{99m}Tc Time of biotechnologies and radioactivity

the key dates remind the fact in few decades from the discovery of the radioactivity we are today speaking about biotechnology, antibodies and immunotherapy.

During what we could call « the Golden Years » 1950 - 1970, a lot of products have been produced and used. Then due to the evolution of the rules and the economical parameters which became more and more important, the actual list of radioisotopes is relatively short. Efforts research and development are on molecules to label with them.

For example, in 1962, the common catalogue for the two nuclear institutes French (CEA) and Belgian (CEN) offered more than 100 isotopes and more than 200 labelled molecules. In comparison, nowadays, only 20 radioisotopes are currently commercialized:

Isotopes used for Nuclear Medicine (non exhaustive list)

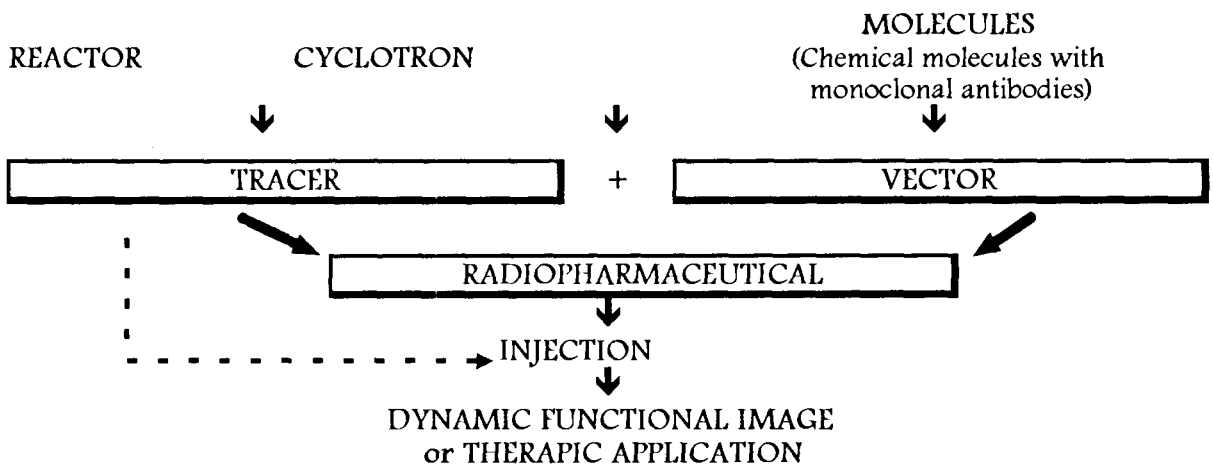
REACTOR	CYCLOTRON
^{99m}Tc	^{201}Tl
^{131}I	^{67}Ga
^{133}Xe	^{111}In
^{125}I	^{123}I
^{90}Y	^{103}Pd
^{186}Re	^{18}F
^{169}Er	
^{59}Fe	
^{51}Cr	
^{153}Sm	
^{89}Sr	

III - MEDICAL APPLICATIONS OF NUCLEAR SCIENCES

III - a) - RADIOPHARMACEUTICALS

The nuclear medicine principle of genesis of a radiopharmaceutical is as follows:

III - a.1. PRINCIPLE



the Producer is dependent of the Reactor disponibility and/or a Cyclotron (with the right specification) and the biology associated to the equipment and its improvement.

The photon or particles emitted by the isotope have to be detected by the existant machines. The shelflife has to be sufficient to reach the target in the body but not too long to minimize the irradiation.

III - a.2. GENESIS OF THE PRODUCT

The radioisotopes are used on its one, or in simple chemical form (examples: $^{131/123}I^-$, $^{201}Tl^+$, $^{99m}TcO_4^-$) or in combination with complex molecules.

All of them are produced artificially from methods briefly described hereafter:

- nuclear reaction induced by fast or thermic neutrons (reactor)

  example: $^{130}Te\ (n,\gamma)\ ^{131}Te \xrightarrow[25\ min]{ß-} {}^{131}I$

- nuclear reaction induced by charged particles (cyclotron)

  example: $^{201}Tl\ (p,3n)\ ^{201}Pb \xrightarrow[9,4\ h]{ß+} {}^{201}Tl$

- by fission (reactor)

  $^{235}U + {}^{1}n \longrightarrow {}^{236}U\ (fission) \longrightarrow {}^{99}Mo \longrightarrow {}^{99m}Tc$

  ^{235}U (enriched ≥ 93%)

For someone, it is possible to use them directly, for others, according to the characteristics of the isotopes, mainly half life, we have been obliged to create and use what we call generator

- ^{99}Mo / ^{99m}Tc generator
- ^{113}Sn / ^{113m}In
- ^{81}Rb / ^{81m}Kr

Most of the time, separation method between father and daughter for these generators is chromatography with organic support such as: Al_2O_3, S_nO_2, Z_rO_2, etc ...

In any case, the products resulting from these processes have to be sterile, apyrogen, non-toxic and several tests have also to be performed:

- radiochemical yield: $\frac{\text{radioactivity measured of the daughter}}{\text{theoretical radioactivity of the daughter}}$
- radionucleidic purity: < 0,1%
- radiochemical purity: *example:* ^{99}Mo / $^{99m}Tc \rightarrow {}^{99m}TcO_4^-$
- chemical purity: *example:* impurities as Al^{3+}

III - a.3. SELECTION OF THE METHOD AND ISOTOPES

As already mentionned, the characteristics of the isotopes determine the choice in study of the new products, in association with the biological specifications of the tissues which constitute the target of the investigation. For instance, for some ovarian tumor, the Indium is the isotope selected for this purpose since the cinetic of accumulation of the vector in a low vascularized tumor and consequently incompatible with Tc (6h / 67h). *Example:* INDIMACIS (CIS bio international) monoclonal antibody OC125 F(ab')2-DTPA for diagnosis of relapsing ovarian adenocarcinoma.

Last example: regarding Technetium, two categories of products could be considered:

- labelled compound having similar characteristics and similar biological way as the compound without labelling (*ex.:* cells, colloïds, proteins, antibodies)
- compounds with biodistribution variable according to the new characteristics of the complex vector-Tc.

- For the labelling different methodes exist and again are fixed by the chemical properties of the components involved and the purpose of the final product.

A non-exhaustive list of methods is:

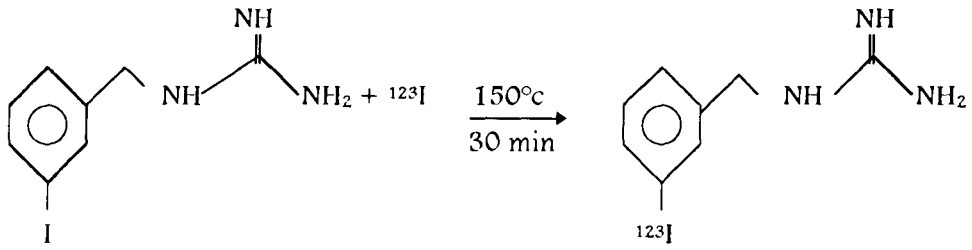
- covalent bound for Tc (peptide, Ab) Tc-peptide or Ab

or

- vector - ligand - Tc

- isotopic exchange for iodine

m-iodo benzylguanidine



To conclude: till now, we are able to visualize a function but not always to quantify it, since we do not know to measure precisely the quantity of the radioactivity present in the organ. A new challenge for specialist and research in Imagery.

Briefly, the two other areas of nuclear medical application are described as follows:

III - b) - RADIOTHERAPY - SOURCES AND EQUIPMENT

THE PRINCIPLE

DESTRUCTION OF TUMOR CELLS THROUGH RADIATION SOURCES

ENDOCAVITARY BRACHYTHERAPY	EXTERNAL RADIOTHERAPY

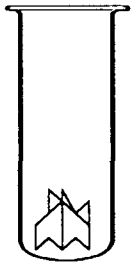
RADIATION IS PRODUCED BY RADIOISOTOPES OR ACCELERATORS
and only three isotopes are currently used

RADIOTHERAPY - SOURCES AND EQUIPMENT

MAIN SOURCES

^{60}Co	CIRUS Theratron
^{137}Cs	Curietron B Curietron AMRA
^{192}Ir	Iridium Wires GAMMAMED

III - c) - IN VITRO DIAGNOSTICS - IMMUNODIAGNOSTICS



PRINCIPLE

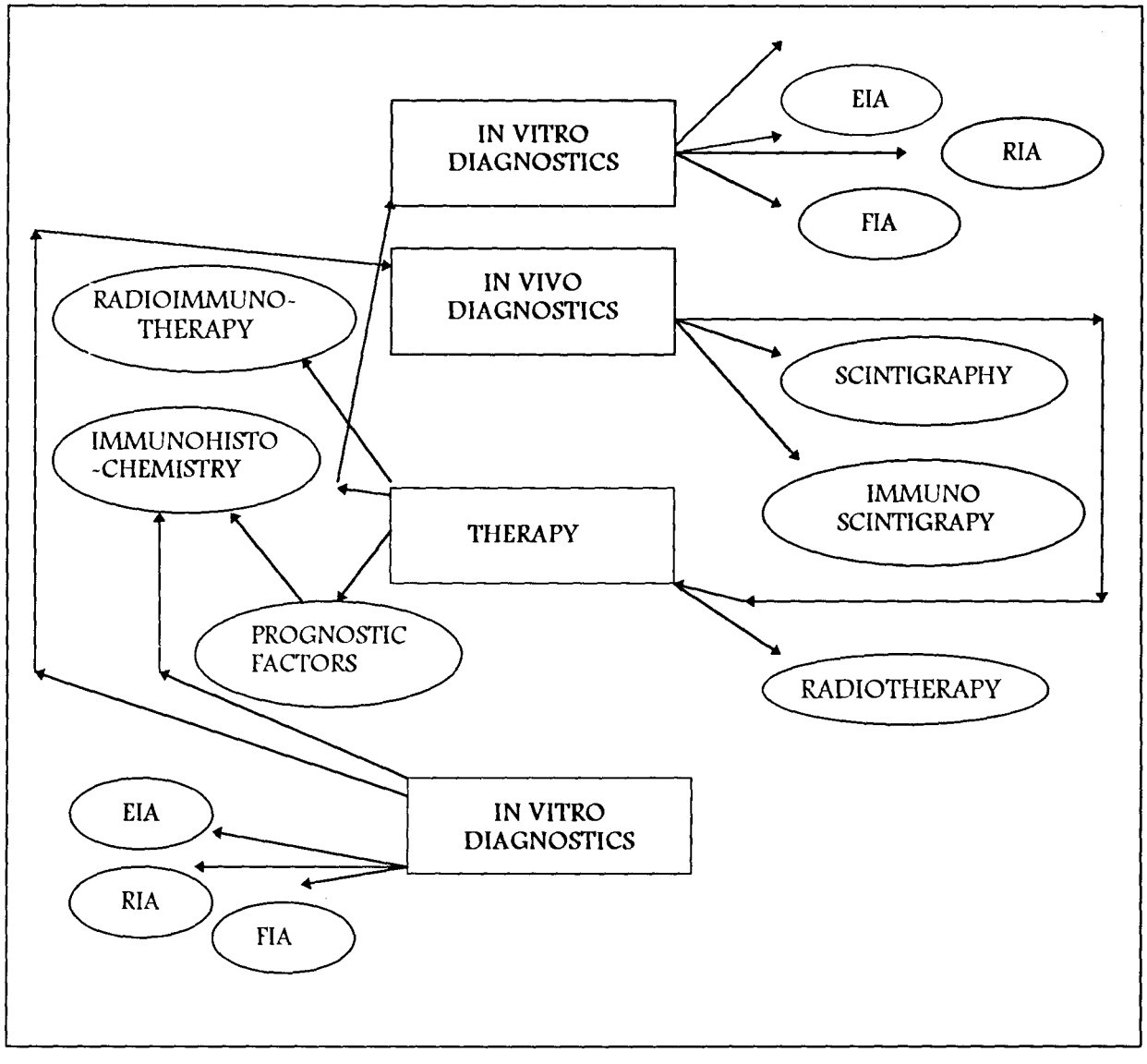
FORMATION OF A COMPOUND:
Ac1 - Ag - Ac2*
↓
Wahsing
↓
MEASUREMENT OF THE TRACER
FIXED ON A SOLID PHASE

The isotope used in this field is ^{125}I.

The quantity for this application is not important comparatively to the medical application, but a high quality is requested.

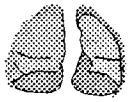
In resumé, the synergy illustrated in the next figure between the three areas is very strong, especially for actors involved in all of them, as CIS bio international.

IN VITRO DIAGNOSTICS - ACM (Monoclonal antibody) - Oncology



IV - SPECIFICITIES OF THE THREE AREAS

IV - a) SPECIFICITIES OF THE EXPERTISES



IV - a.1. Nuclear Medicine Radiopharmaceuticals

Expensive industrial investments

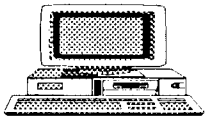
Important and increasing regulatory constraints: pharmaceutical, nuclear

LIFE DURATION OF A PRODUCT > 10 ans

IV - a.2. Therapy Sources and Equipment

Expensive industrial investments

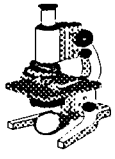
Important regulation constraints: transportation, treatment of radioactive waste ...



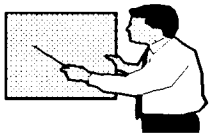
Necessity of plurality skills: nuclear, mechanical, data processing, systems

LIFE DURATION OF A PRODUCT > 10 years

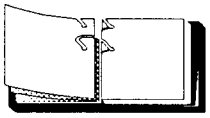
IV - a.3. In Vitro diagnostics Immunodiagnostics



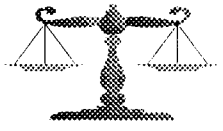
Strong innovation
➔ High R & D potential



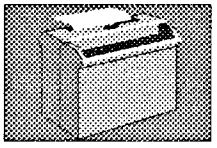
Duration of gestation of a system:
5 to 10 years



Life duration of a product:
5 to 7 years



Strong economical pressure
➔ Health policies
➔ Price pressure



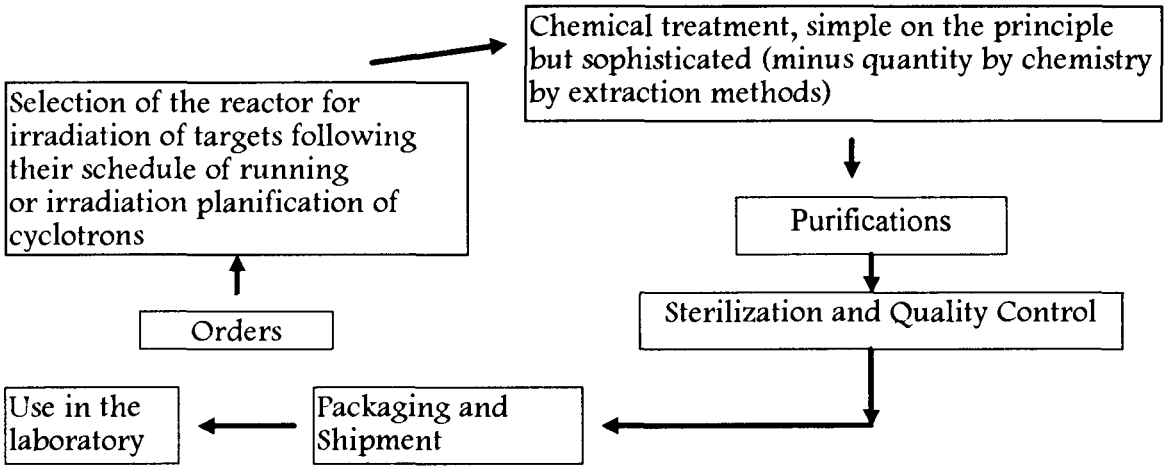
Trend towards systems
➔ Reagents + equipment

IV - b) PRODUCTION ASPECTS

The first priority for the people involved in nuclear medicine is the medical function and respect of the patient. So quality and time of delivery of the product have to be respected. Consequently each need from the hospital is transformed instantaneously in an order to the producer. From this time, it is a race against the clock. The objective is to deliver the product in 24 hours or in three days maximum, anywhere in the world.

So, due to the worldwide expansion of this speciality, the time to deliver the product with a bicycle after a friendly conversation between the doctor and the researcher is totally finished.

We can resume as follows the production and shipment diagram:



To practice this cycle efficiently and reliable, 365 days a year, the manufacturers have developped an agenda for the availability of the products, the connection with the forwarders and airline companies, education of all job involved in shipment. Nowadays, the logistic is in the heart of the success and the key point for offering a good service.

So for a radiopharmaceutical producer, the key points for ensuring production and the delivery are to follow the nuclear safety rules, inside the facilities, during the transportation and in users sites.

For example, such a company like CIS bio international ship roughly 20.000 parcels/month in 60 countries by trucks, trains and planes.

We are totally entered in an industrial era.

IV - c) THE EVOLUTION OF THE NUCLEAR MEDICAL APPLICATION

For example the companies or producers in a general term of radiopharmaceuticals have to acquire and did it, a good capacity in clinical research and clinical monitoring.

Licensing of the radiopharmaceuticals has become very expensive and time consuming. A very rough estimation indicate that when a potential molecule has been identified, approximatively 2-3 millions of USD has to be spent before the first clinical step. In despite these specificities which could appear restrictive, the radiopharmaceuticals or the nuclear medicine world is evoluting.

The following figures show the evolution and development of the market:

Table 12
WORLD NUCLEAR IMAGING

Year	Radiopharmaceuticals	Gamma Cameras	Other	Total Market
1995	$1.1 billion	$500 million	$100 million	$1.7 billion
2000	$1.7 billion	$600 million	$300 million	$2.6 billion
2005	$2.7 billion	$700 million	$500 million	$3.9 billion

Note: 1. European radiopharmaceuticals in 1995 were $500 million. forecast to $900 million by 2000
2. Others include PET and SPECT systems

In the next figures, we can see the change in the European legislation showing in parallel interaction between standard products and high tech products.

RADIOPHARMACEUTICALS IN EUROPE

PHARMACEUTICALS	BIOTECHNOLOGY
1965 - Directive 65/65/EEC related to pharmaceuticals	
1975 - Directives 75/318 - 75/319 75/320 Complete 65/65/EEC Exclude radiopharmaceuticals	
	1987 - Directive 87/22/EEC High tech products for human use
1989 - Directive 89/343/EEC extend 65/65/EEC to radiopharmaceuticals	

1991 - Notes related to:
. Radiopharmaceuticals
. Radiopharmaceuticals based on M.Ab

1992 - Notes to applicants:
EC filing format for biotechnologies products (including radiopharmaceuticals)

CIS bio international

In order to manage such an evolution and succeed to reach the new challenge, we can see around the world some new association as for example in Europe the creation in 1992 of ARPE (Association for Radiopharmaceutical Producers in Europe)

ARPE'S OBJECTIVES

- To represent the common interest of the members in relation with European Community and with other national and international authorities.
- To increase the awareness of the benefits of radiopharmaceuticals.
- To represent its members in dealing with other scientific, educational or professional association groups or societies, such as EANM, EFPIA.

CIS bio international

CONCLUSION

In despite of the restrictive parameters such as the safety rules, reduction of health care costs, the nuclear medicine is increasing and generally integrated in all new nuclear project including a research reactor (example: Morocco, Thailand ...).

Associated to the high technologies, Imagery, Immunology and molecular biology, the Nuclear Sciences participate in the future of the medicine.

The key points determining the structure and the organization of this world and actors are:

- switch from epoch of research to epoch of industry with the consequence of epoch of mergers
- health care cost $\Rightarrow$ a worldwide phenomenon
- legislative and ecology $\Rightarrow$ survey in multiplication of production sites and cause of the definitive stops of some one

In all new project, these elements constitute the guide in the adventure of the nuclear medical applications.