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HISTORY OF MEDICINE – REVIEW – OPEN ACCESS

A Recent History of Ultrasound Contrast Media and Nuclear Medicine Tracers

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ABSTRACT

The recent developmental history of contrast media and nuclear medicine tracers has been crucial in facilitating the innovation of radiology equipment. Modern ultrasound has provided an opportunity for developing gas-encapsulated contrast products. In addition, scintigraphy has also evolved with "technetium cows," especially in cardiology. However, the revolution in nuclear medicine arrived with the use of positron emission tomography with Fluorine-18 fluorodeoxyglucose (18F-FDG) in this field, followed by new and numerous other products and radioelements such as gallium-68 and the corresponding generators. To highlight the lesser known history of ultrasound contrast media and nuclear medicine tracers, this review indicates the success of its progress over the last decades, at least at the university level. It has enabled radiological practices to evolve and accompany the technological innovations in imaging equipment. In all fields, patients have been able to benefit from the knowledge acquired for improving the diagnosis and therapeutic management of their pathologies. As for other imaging techniques, however, a significant slowdown in innovation was observed because of the difficulties associated with applications for the marketing authorization of diagnostic imaging products and the low return on investment for the concerned manufacturers.

Keywords: Contrast media, echography, history of medicine, history of pharmacy, nuclear medicine, ultrasonography

INTRODUCTION

The last decades have been a proud witness to numerous discoveries in radiology. Some of discoveries had a short life or were even unsuccessful. However, all of them were successful in stimulating the research and the imagination of radiologists and researchers (1). A previous study showed that over the last century, the contributions of suitable contrast products with improved diagnosis and patient management have greatly benefited imaging using X-rays and magnetic resonance imaging (MRI) (2). Two other imaging techniques have been developed in ultrasound and nuclear medicine, and both have also prompted active research to find suitable products for these technologies (3, 4). Contrary to ultrasound, where the use of contrast products remains very limited, nuclear medicine tracers are essential for using this technique (5). To highlight the lesser known history of ultrasound contrast media and nuclear medicine tracers, this review aims to cover their success in last four decades.

Contrast Agents in Echography

As with other imaging techniques, it was believed fairly quickly after the discovery of ultrasound imaging (echography) that products could be useful for modifying the signal, increasing contrast, or characterizing the lesions detected by this technique. Although this ultrasound imaging technique dates to the 1950s, Gramiak et al. (6) introduced contrast ultrasound and had noticed the appearance of "clouds of bubbles" during the flushing of catheters in the aorta. Other researchers then initially tested several products such as saline after agitation, indocyanine green solution, ether, carbon dioxide, diatrizoate, and so on (7, 8). In the 1980s, researchers had considered different approaches. An American researcher, Steven Quay, developed a product based on Dodecafluoropentane (9). The product received a marketing authorization (MA) in Europe in 1998 but was never marketed. However, there have been other works actively undertaken in this field. In 1991, Schering marketed the first ultrasound product, Echovist®, based on galactose and, then, an improved version, Levovist® (10).

However, the poor efficacy of these first products led the development of a new generation of contrast agents, generally comprising gas microbubbles stabilized by biocompatible materials (proteins, lipids, polymers). Their size varies from 2 to 10 microns (Table 1). The first of these, Albunex®, was based on Albumin (air-filled capsules), as was Optison®, which was introduced a few years later. Other products (microcapsules) were developed based on perfluorocarbons gas (Definity®) or sulfur hexafluoride (Sonovue®) where the air was replaced by perfluorocarbons for improving the duration of their presence in the blood (11). The latter product, marketed in Europe by Bracco Laboratories since the early 2000s, is used for echocardiography, Doppler examination of microvessels and, more

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Table 1. Contrast agents used for echography in some countries

Name of the product (company)	Composition (gas)
Echovist® (Schering)*	Galactose (air)
Levovist® (Schering)*	Galactose (air)
Albunex® (Molecular Biosystems)*	Albumine (air)
Optison® (GE Healthcare)	Albumine (octafluoropropane)
Echogen® (Sonus Pharmaceutical)*	Sucrose (dodecafluoropentane)
Definity® (Lantheus Medical Imaging)	Phospholipids (perfluorocarbone)
Imagent® (IMCOR Pharmaceuticals Inc)*	Phospholipids (perfluorohexane)
Sonovue® (Bracco)**	Phospholipids (Hexafluorure de soufre)

*: Commercialized in Europe; **: Not commercialized in the USA

recently, excretory tract ultrasound. The European Federation of Ultrasound's guidelines offered the main vascular indications for this technique: carotid pathologies, abdominal aorta, and cerebral vessels (12). However, the practical use of these products remains limited, despite the numerous scientific publications in this field, and represents less than 5% of the contrast product market.

Failures and Prospects in Ultrasound

In the field of contrast products for ultrasound, sales remain very limited than the products for other imaging techniques. However, research is continuing with the development of nanometric-sized products, thereby allowing for a better persistence in the blood with or without the incorporation of polyethylene glycol. Trials where nanoobjects are associated with specific ligands such as HER2 or EGFR or with monoclonal antibodies are also underway (13). The use of ultrasound contrast products for therapeutic applications is also being considered, as microbubbles-containing therapeutic agents can be destroyed under the effect of ultrasound in a specific organ or pathology to release their contents (14).

Tracers in Nuclear Medicine

What characterizes this field is that tracers are indispensable: there is no image without tracers. Nuclear medicine uses the radiation emitted from the nuclei of radioactive atoms administered to patients. Its origins can be traced to Henri Becquerel (1852–1908) who discovered radioactivity from uranium in 1896. In 1903, he received the Nobel Prize in Physics along with Pierre and Marie Curie who had discovered the radioactivity of thorium, radium, and polonium (15). However, Frédéric Joliot-Curie took a decisive step with the discovery of artificial radioactivity in January 1934 (16). Three years later, Joseph Hamilton became the first person to use these radiotracers to study the physiology of the circulation with radioactive sodium and later became the first person to measure Iodine uptake in the thyroid using Iodine-128 (17). Iodine-131 was first used in 1940 for diagnosing hyperthyroidism (18). Emilio Gino Segrè discovered technetium-99 m in 1938 (19).

Conventional scintigraphy, based on the use of gamma emitting tracers, was the only imaging technique used for a long time; moreover, it still represents 80% of the diagnostic examinations in nuclear medicine. The main element used at 80% is technetium (99 mTc) prepared from molybdenum-99, which is largely supplied by nuclear reactors. Produced by the famous "technetium cows" in hospitals, this key element is complexed with different chelates depending on the objective. The most important in terms of volume is undoubtedly the production of sestamibi, mainly for myocardial perfusion explorations that have been competing with thallium-201 in this field for the past three decades (20). However, other chelating agents are used for technetium for other explorations (Table 1). Overall, this is a field that has been stable for several years with two key areas, namely, cardiology and bone pathologies.

Nuclear medicine tracers for diagnosis have undergone unprecedented development over the last two decades, in particular with the advent of positron emission tomography (PET) and hybrid single-photon emission computed tomography (SPECT)/computed tomography (CT), SPECT/MRI), PET/CT, and PET/MRI equipment (21, 22). PET examinations have increased sharply from 167,000 in 2009 to 496,000 in 2018 in France out of a total of 1.6 million diagnostic nuclear medicine examinations in the same year. Over this period, there were more than 90% of the examinations with 18F-FDG (Table 2).

Over the last four decades, research has developed significantly for PET imaging, mainly around two radionuclides, namely, Fluorine 18 and Gallium 68. Work on 18F-FDG dates to 1976 when the first synthesis was conducted at the Brookhaven Laboratory (USA). However, it was not until several years later that it was available in radiology departments, as this required the development of suitable equipment (23). In France, Cis-Bio, a CEA company, was the first to market 18F-FDG at the end of the 1990s, followed by many competitors from 2002. The indications are very broad: oncology, cardiology, neurology, infectious or inflammatory diseases. The second product marketed was FNa (sodium fluoride-F18) for pathologies "where an alteration of osteoblastic activity is sought," from 2008 by the company Iason GmbH, which was also rapidly challenged by other companies from 2010. The same company also marketed a dopamine derivative in neurology and oncology in 2006, a choline derivative for diagnosing bone metastases of prostate cancer and hepatocellular carcinoma in 2010, and a fluorinated tyroxine derivative (Iasoglio®) for the characterization of gliomas in 2015, which is often copied by other companies. Fluoroestradiol (18F), for its part, obtained its MA in France in 2016 and in the USA in 2021 for the "characterization of known or suspected metastatic lesions expressing estrogen receptors in adult breast cancer initially expressing the estrogen receptor." In addition, 18F-fluciclovine (Axumin®, BED-Bracco) obtained its European MA in 2017 for detecting prostate cancer recurrence and is marketed in several European countries. These few examples show that new products based on Fluorine 18 have been marketed over the last two decades. However, this observation does not represent the very large amount of research conducted at the university level in this field that has not led to MA (Table 3) (24).

The other major area of research in PET has revolved around gallium-68. This element has a short half-life (68 minutes) and has the advantage of being produced, not by a cyclotron like Fluorine-18 but by a generator from germanium-68 (like 99 mTc from molybdenum 99). If such a generator is available at the patient's bed, then images can be made by complexing the produced gallium. This research will lead to the approval of a first gallium-68 generator in 2015 (Galliapharm®, Eckert & Ziegler) and the first products approved in 2016 for PET imaging with gallium

Table 2. Tracers used in nuclear medicine for diagnosis

Conventional scintigraphy	
Technetium ^{99}mTc	HMDP (hydroxymethylene diphosphonate of sodium, scintigraphy of the skeleton, Sestamibi, Tetrofosmine (myocardial perfusion, parathyroids, breast tissues), Angiocis (ventricular ejection fraction, search for bleeding, Pertechnetate (thyroid function), HMPAO (hexa-methyl-propylene-amine-oxime, brain perfusion), etc.
Thallium ^{201}Tl	thallium chloride (201Tl) for myocardial perfusion, parathyroids glands, etc.
Krypton (^{81} mKr)	Kryptoscan®, pulmonary ventilation
Iode ^{123}I	DaTSCAN® Ioflupane (dopaminergic neurotransmission); MIBG (méta-iodobenzylguanidine) or iobenguane, medullo-adrenal gland
Iode ^{131}I	Noriodocholestérol, adrenal cortex
Indium (^{111}In)	Pentétréotide, somatostatin receptor (neuroendocrine tumor)
PET	
^{18}F-FDG	Glucose metabolism (Glucotep, Fludesoxyglucose, Gluscan, etc)
^{18}F-FCH (fluorocholine)	Membrane lipid metabolim (Prostatep, Iasocholine, etc.)
^{18}F-(fluorure or FNa)	Skeleton
^{18}F-FDOPA	Amino acid metabolism, Dopaminergic neurotransmission (Dopacis, Dopaview, Iasodopa, etc.)
^{18}F-PSMA	Prostate (on going approval)
Other radionuclides	^{68}Ga,^{82}Rb, ^{11}C, ^{13}N, ^{15}O

PET: Positron emission tomography

Table 3. Some key events in the history of nuclear medicine (1987–2008)

Year	Historical development
1987	Medi-Physics receives FDA approval to market the first radiopharmaceutical brain perfusion tracer, Iodine 123-IMP.
1988	Introduction of the first Tc-99 m radiopharmaceutical by Amersham for diagnosing stroke.
1989	FDA approval of the first rubidium-82–based tracer for myocardial perfusion.
1990	Steve Lamberts and Eric Krenning performed imaging of endocrine tumors using somatostatin-binding radiotracers.
1990	First FDA approval for a Tc99 m-based myocardial perfusion marker.
1992	FDA approval of the first radiolabeled monoclonal antibody for tumor imaging.
1994	Mallinckrodt receives FDA approval to market the first radiolabeled somatostatin receptor peptide for imaging autoimmune diseases.
1996	Acceptance of brain PET.
1997	Validation of 123I-beta–CIT for the evaluation of dopamine transporters for diagnosing Parkinson's disease.
1998	FDG-PET is used to assess response to chemotherapy.
1999	First commercial PET/Scanner.
1999	Approval of Cis-Bio's technetium-99 m-labeled sodium pyrophosphate decahydrate for the in vivo labeling of red blood cells in France.
1999	Approval in France of Cis-Bio's anhydrous sodium phytate for liver scintigraphy.
2000	Marketing in France of technetium-99 m-labeled mebrofenate for hepato-biliary scintigraphy.
2001	16.9 million nuclear medicine examinations are performed that year in the United States.
2008	Installation of the first hybrid PET-MRI machine for patients, from Siemens, followed by the one from General Electric in 2013.

FDG: Fluorodeoxyglucose; PET: Positron emission tomography; MRI: Magnetic resonance imaging

for neuroendocrine tumors (68Ga) edotreotide (Sogacin®, ITG GmbH and Somakit®, Gipharma S.r.l.) (25). These 68Ga-labeled products are intended to select patients who can benefit from a very expensive treatment with Lutecium (177Lu oxodotreotide, Lutathera®). Numerous molecules are currently undergoing clinical research in this field of 68Ga (26). The installation to accommodate a gallium generator requires meeting the reinforced technical and regulatory constraints, in particular the provision of 4 RDG enclosures of more than 8 tons.

Cyclotrons can also produce other potentially interesting radionuclides such as C11, N13, 015, and Rb82 but the half-life of these elements presents more difficulty in their handling (27). In contrast, 64Cu has a half-life compatible with a more realistic use in routine (Table 4).

Table 4. Half-life of radiotracers in PET

Radiotracer	Half-life (minutes)
F-18	109.8
C-11	20.4
N-13	9.98
O-15	2.03
Ga-68	68.0
Rb-82	1.3
Cu-64	762

PET: Positron emission tomography

Major Innovations: SPECT/CT, PET/CT, and PET/MRI

Three successive revolutions, namely, the introduction of SPECT/CT in 1999, PET/CT in 2000, and PET/MRI in 2008, have put nuclear medicine at the forefront. All these hybrid modalities have shown their superiority over nuclear medicine alone (SPECT or PET), both in oncology and in the field of pulmonary, infectious, or other pathologies (28). However, it is in the field of PET/MRI that bi- and tri-modal tracers have been extensively studied over the last decade, without leading to a commercial product (29).

First, in the early 2010s, hybrid products based on DOTA-gadolinium on the one hand, and fluorinated organic molecules F-18, on the other hand, were devised for the purpose of tumor labeling (29). Other products have combined gadolinium and PET/SPECT tracers such as copper, gallium, or indium. Another avenue of research has been to explore the association of superparamagnetic iron oxide (SPIO) particles with radioelements in complexed or non-complexed form. One approach has been to use DOTA to complex Cu-64 and to combine it with pegylated SPIO particles on the surface, the constraint being however to find concentrations suitable for both PET and MRI and compatible pharmacokinetics. Polyaspartic acid-linked SPIOs were also combined with integrin-targeting peptides, with the combination combined with DOTA–Cu-64 to image tumors expressing αβ integrins. To avoid capture by the reticuloendothelial system, other investigators have used ultrasmall superparamagnetic iron oxide particles combined with Cu-64, Zn-89, or Ga-68, with or without complexing agents (29, 30). Carbon nanotubes associated with radionuclide complexes have also been used. Finally, contrast agents have been developed to modify the signal in three modalities: PET, MRI, and optical imaging (fluorescence). For example, there have been attempts to associate a gadolinium complex with a fluorescent prophyrin carrying Cu-64 (31). These complex multimodal approaches would allow several imaging modalities to be performed simultaneously.

This is not the only revolution that has changed the landscape in the last two decades. There has also been a significant change on the industrial aspect for technical and financial reasons. First, on the technical level, the production of molybdenum, the source of technetium, has been very irregular over the last two decades due to the obsolescence of the nuclear reactors that produce it, particularly around 2010. The Canadian Chalk River reactor that served the United States closed in 2018, and the CEA reactor in France, Osiris, was already closed in 2015. This situation led to the creation of a joint effort by the OECD and the Nuclear Energy Agency to find a way to supply sufficient molybdenum-99.

Among the solutions implemented, cyclotron production has been developed and would eventually avoid the need for nuclear power plants. However, this solution appears difficult to implement, given the low production yields. In contrast, Shine in the United States is continuing its research into producing molybdenum-99 without using a nuclear reactor. The other factor that has contributed to reshaping the industrial landscape was the appearance of PET, the relative stability of conventional nuclear medicine because SPECT is still mainly used for cardiology (Mibi and Thallium-201) and by bone pathologies (DTPA 99Tc), and the first generics of BMS' Cardiolite® in 2008 (sestamibi, for myocardial perfusion), which dominated the technetium market. These phenomena have caused a sharp reduction in manufacturers' margins, further leading to the consolidation or sale of traditional market players such as BMS (USA), Mallinkrodt (USA), and the appearance of newcomers, such as Curion, Lantheus, and many more.

Failures and Prospects in Nuclear Medicine

Despite a great deal of research, only a proportionally few new products have been marketed in the field of nuclear medicine. In addition to the cost of development, several researchers have pointed out the regulatory difficulties and the fact that the guidelines in both Europe and the United States are poorly adapted to the particular case of PET and markers in this field (32, 33).

In contrast, we can see that the research areas opened up by PET and PET/MRI facilitated the rise of abundant research at the university level since the early 2000s. Moreover, we can expect this research to continue in the coming years, for example with Iodine I-124, Cu-64, and hybrid products. However, their price level remains the major problem with these recent products, and it may or may not be accepted by the health authorities and it delays or even prevents their commercialization in certain countries.

CONCLUSION

This review of the last few decades of research and development in the field of ultrasound contrast products and nuclear medicine tracers demonstrates how fruitful this work has been, at least at the university level. It has enabled radiological practices to evolve and facilitate the technological innovations in imaging equipment. In all fields, patients have been able to benefit from the knowledge acquired to improve the diagnosis and therapeutic management of their pathologies. However, as for other imaging techniques, there has been a significant slowdown in innovation due to the difficulties associated with applications for MA for diagnostic imaging products and the low return on investment for the concerned manufacturers.

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