VOL 1 • NO 2

ePATIENT

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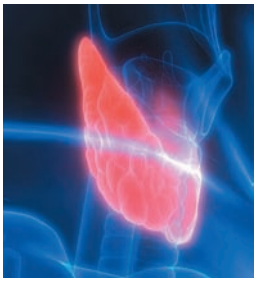

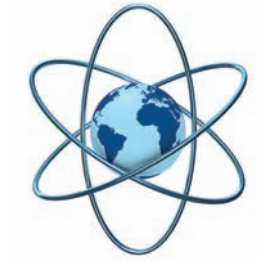

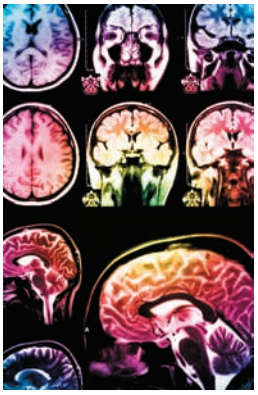

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Don't miss our next issue on Quantification and the second part of Theranostics (neuroendocrine tumors).

EDITORIAL BOARD

Dr. Lamoureux and I are thrilled to introduce our outstanding editorial board members. Through our travel and NM lecturing around the globe, we have met terrific scientists and colleagues. Most, if not all of them, are really passionate about and true advocates for the field of nuclear medicine. They strongly believe in the power, usefulness and safe use of NM diagnostic and therapeutic procedures for the betterment of public healthcare worldwide. We are delighted that the following leaders have embraced the concept of the Pangea-ePatient magazine and accepted to share their invaluable expertise and experience with patients, referring colleagues, health care administrators, government agencies and insurance companies.

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INTRODUCTION TO THE SECOND ISSUE

François Lamoureux
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Past President, CANM

François Lamoureux and I are pleased to introduce the second issue of the acclaimed Pangea-ePatient magazine.

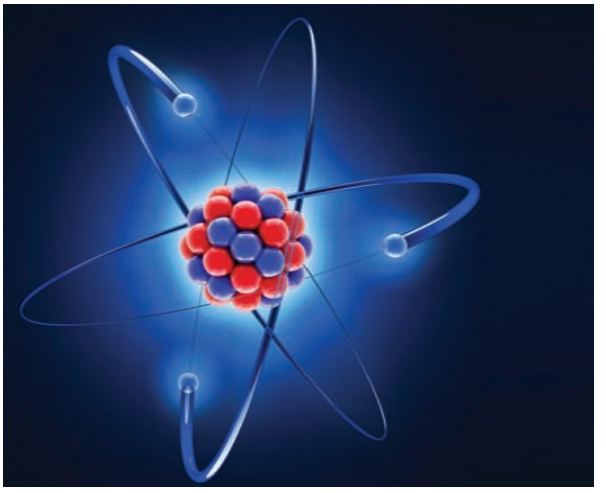
As you know, the idea behind the Pangea project and Pangea-ePatient magazine is to educate prescribing physicians, patients, health authorities and hospital administrators from across the world about current and future nuclear medicine diagnostic tests and therapies in comprehensible words.

With the endorsement of most of the large regional and many national associations of nuclear medicine, we are delighted to welcome on the editorial board five new members. With the addition of Drs. Al-Ibraheem, Mohamad Haider, Rodrigo Jaimovich, Christian Scheiber and Andrew Scott, the magazine will provide an even broader international "pangean" perspective and audience to illustrate the benefits of the safe use of medical isotopes in the management of patients' diseases.

In this new issue, you will find articles in English, French, Spanish, Chinese and Arabic (digital version only at this point). Besides the interviews of international leaders in the NM field like Dr. Danfer Huapaya, President of the Latin American Societies of Nuclear Medicine, we have asked colleagues from across the world to share their experience and expertise in brain scintigraphy and the treatment of thyroid cancers. The thyroid cancer section will in fact represent the first part of a series on Theranostics. In the next two issues of the magazine that are scheduled to be published in June and October we will have articles on neuroendocrine tumors and prostate cancers, respectively.

The Pangea-ePatient publication is largely digital and available with easy access and download on electronic platform such as smartphones, tablets, laptops and desktop computers at nmpangea.com in more than 100 different languages. Limited hard print copies can also be obtained on demand or at the CANM kiosk at the following annual conferences: CANM, SNNMI and EANM and at the 2018 WFNMB congress in Melbourne.

We sincerely hope that you will enjoy this new issue of the magazine. We would love to hear your comments and criticisms to further improve the content and format of the premiere international nuclear medicine educational magazine.



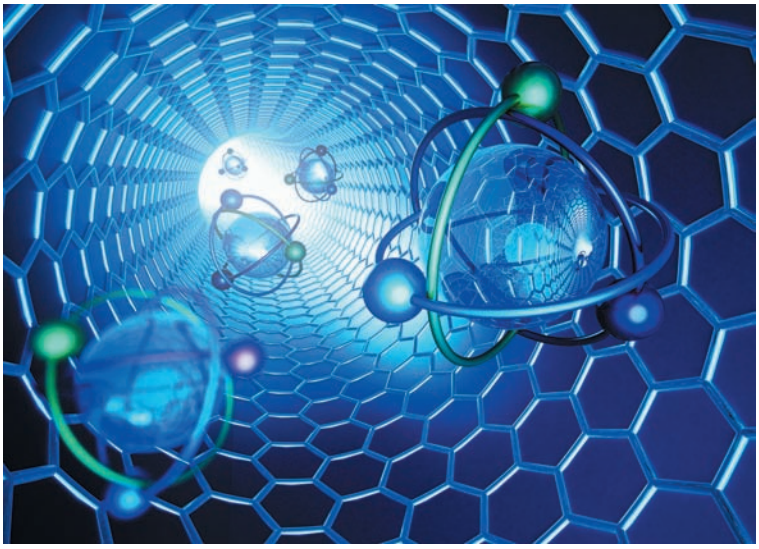
Jean-Luc Urbain
M.D., Ph.D., CPE
Past President, CANM

THERANOSTICS:
NUCLEAR MEDICINE AT ITS BEST

In this new issue of Pangea-ePatient we are starting a series of articles on radio-pharmaceuticals that are used for diagnostic and therapeutic procedures that are now commonly called Theranostics.

Theranostics, the new buzz word in medicine was coined in the early 2000's by the CEO of PhamaNetics to define the vision for his company. It stems from the contraction of two words: therapeutics and diagnostics. Theranostics are one of the significant outcomes of the Human Genome Project. In the medical era of the omics, it is directly related to, if not synonym to, personalized medicine where diagnostic and therapeutic procedures are individually carved out for patients based on their genotype and phenotype. Most commonly, it refers to the use of a single agent/compound to diagnose and treat a specific disease.

While fitting well with the medical vocabulary of the new millennium, Theranostics are not new to nuclear medicine practitioners. In fact, it has been intimately part of our day to day practice for a long time. Way before the sequencing of the sodium iodine symporter gene in 1996 which characterized the cellular membrane transporter for iodine., nuclear medicine had already used the same physiologic 131 iodine molecule to diagnose and to treat patients with thyroid cancer for a few decades. Radioiodine imaging of the thyroid gland was in fact initiated by Benedict Cassen in 1950 already at UCLA using, at the time, a rectilinear scanner. To this day, the accumulation or lack of uptake of radioiodine by the thyroid gland represents a key non-invasive tool for the diagnosis and treatment of thyroid cancers.



The visualization, description and quantification of the molecular processes in normal and abnormal cells through molecular techniques has exploded since the late 1990s. Modern therapy of cancers, neurological and cardiac conditions now relies on the identification and targeting of specific cellular molecules. At the intersection of molecular biology and imaging, molecular imaging and nuclear medicine have grown exponentially as the complex biochemical and molecular secrets of the cell were being unraveled. The number of articles and references already published on the subject is striking: in less than 1 second a Google search for the words molecular imaging yields more than 8.6 million hits.

Using specific probes and labeling them with diagnostic and/or killer medical isotopes, nuclear medicine offers the most attractive and quintessential tool in theranostic medicine. Besides iodine, the second class of nuclear medicine compounds that can fall into theranostic nuclear medicine are the radiolabeled monoclonal antibodies and their fragments' variations. Unfortunately, and albeit having an exquisite specificity to targets, their high molecular weight, slow clearance and poor diffusion in the tissues did severely limit their clinical usefulness. In vogue in the 80's and early 90's the only three "survivors" of that chapter of nuclear medicine that are in clinical use today are the anti CD20 idodine-131 labeled tositumomab (Iodine-131 Bexxar) and Y-90 ibritumomab tiuxetan (Zevalin) and the almost defunct Indium-111 Capromab pentedite monoclonal antibodies.

The modern landmark for theranostic nuclear medicine originated in the seventies with the discovery of Somatostatin. Somatostatin, a 14-

amino acid Cystin bridge-containing peptide, was first discovered in 1973. The elucidation of its three-dimensional structure, its metabolism and biological activity site in the following years rapidly lead to the synthesis of a large number of analogs. Identified as the most stable and active in inhibiting the effect of the growth hormone, Octreotide, one of the derivatives, demonstrated enough in vivo stability to obtain regulatory approval in 1988 for the treatment of acromegaly and carcinoid tumors.

The coupling of Octreotide to gamma emitting isotopes in the late 80's and early 90's represented a major breakthrough to what we call now molecular targeted imaging. Furthermore, its labeling with yttrium 90 and lutetium 177 in the early 2000's started the modern era of theranostic nuclear medicine by introducing the fast-growing field of peptide receptor radionuclide therapy (PRRT). In PRRT, specific receptors present at the surface of tumors can now be detected, imaged, treated and followed up with the same peptidomimetic labeled with either imaging or killer isotopes. Labeled with gallium 68, a positron emitter and lutetium 177 a gamma and beta emitter, the somatostatin analog dotatate has recently emerged as a prime tool to diagnose, treat and follow up the treatment efficacy of neuroendocrine tumors overexpressing the somatostatin receptor.

High throughput platforms such as phage, bacterial and aptamers display libraries, protein, RNA and DNA microarrays, fluorescence, spectroscopy are now routinely used to identify and to develop small molecular probes to image and potentially treat these specific receptors targets. Tagged with bifunctional chelating agents, native peptides, hormones, neurotransmitters and peptidomimetics are now emerging as suitable molecules for site-directed targeted imaging and therapy. Among the most promising of these compounds in nuclear medicine are the inhibitors of the prostate specific membrane antigen (PSMA).

PSMA is a membrane glycoprotein with peptidase activity which is significantly over-expressed in prostate cancers. Its expression increases with tumor aggressiveness, androgen-independence, metastatic disease, and disease recurrence. Evidence suggests that PSMA may perform multiple physiological functions within the cell: a role in signal transduction, cell migration, receptor function for an unidentified ligand and nutrient uptake such as glutamate and folate have been suggested.

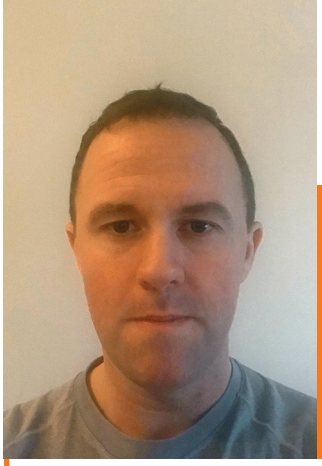
Having a sensitive and specific biomarker to localize primary and metastatic prostate cancer would greatly improve the algorithm for the diagnosis and management of prostate cancer. Other than skin cancer, prostate cancer is the most common cancer in North America. There are about 180,890 new cases of prostate cancer every year in the US. About one out of seven men will be diagnosed from prostate cancer during his lifetime.

Since 2012, the number of clinical studies using urea-based PSMA ligands, such as 123, 124, 131 labeled IMIP-1072/-1095, 99mTc labeled MIP-1404/-1405, 68Ga labeled HBED-PSMA, 18F labeled DCFBC and DCFPyl, has exponentially increased. Among these agents, the 68Ga- and 18F-labeled compounds have attracted the most attention, as these compounds can be used for PET/CT imaging. However, the availability of 123I or 99mTc also will allow SPECT/CT imaging in centers without facilities for PET. Based on these studies, the promising uses of imaging with labeled PSMA ligands in the management of prostate carcinoma include: the primary staging of high risk cancer disease, the biochemical recurrence with low PSA levels (as low as 0.2 ng/ml), identification of lesions for biopsy targeting after negative previous biopsy, the monitoring of systemic treatment in metastatic disease, the active surveillance and the treatment monitoring after 177Lu-PSMA ligand therapy.

Because of their ability to characterize cellular physiology and dysfunction, the radio-pharmaceuticals used in nuclear medicine offer a very unique and specific window on disease that can exploited both for diagnostic and therapeutic purposes. During the past two decades, numerous ligands that bind to specific molecular targets, particularly in cancers, have been identified and characterized. Their labeling with single photon and positron emitters and alpha or beta particles has opened up a new era in nuclear medicine. While still in its infancy, nuclear diagnostic and therapeutic targeting (nuclear theranostics) is rapidly becoming a cornerstone in personalized oncology medicine.

The lack of concerted efforts in research and development of new radio-pharmaceuticals in the last part of the 20th century created a climate of uncertainty about the field of nuclear medicine at the eve of the 21st century. In a very interesting and remarkable turn of events, theranostics have the potentials of becoming the new holy grail of nuclear medicine.

In this issue, we will first look at the treatment of thyroid cancers with radioiodine. The upcoming June 2018 issue will illustrate the use of Theranostics in neuroendocrine tumors. In the October 2018 edition, we will describe and illustrate the very exciting new radiopharmaceuticals for the diagnosis and treatment of prostate cancers.



Interview with: Jonathan Richardson

Chief Technologist, Nuclear Medicine
Wake Forest Baptist Medical Center

You have been involved in NM for many years. What are the most significant changes that you have seen in the field of NM over the past few years?

I started out as a staff technologist in 2003. When I first began in Nuclear Medicine, myocardial perfusion imaging, gallbladder, thyroid imaging with treatment, bone scans, and VQ scans were the bread and butter of Nuclear Medicine. The hospital where I began my career was a large community hospital, with a goal of creating a cancer center. At the time, PET-CT was becoming a main target for every hospital to acquire with the potential and of course as we all know, the massive advantages to patients it has delivered. I saw this as a win for patients and really was inspired by the way the administrators set a goal, and acquired our PET scanner, the first in the area.

The department of nuclear medicine at Wake Forest has always been at the fore front of innovation in NM. What are the major challenges and opportunities that you envision for the department over the next 5-10 years?

I feel as a manager now, you must monitor upcoming procedures, equipment, as Nuclear Medicine is lower profiled compared to MR or CT. With Nuclear yielding lower volumes of patients that other modalities, it is challenging to convince hospital administrators of the need for equipment in the world we live in today with constrained budgets. New therapies show great promise; however, they are often expensive so having venders work with your authorization and reimbursement departments will help ease any issue with cost. With imaging such as VQ scans, 3 phase bone scans, and MUGA scans fading away due to going to other modalities, Nuclear Medicine must focus on therapies that MR and CT cannot offer. Y-90 Sirspheres is a great example of a therapy that shows great outcomes, with providing data on how much dose was delivered to different areas of the liver, to improve treatment going forward. With Nuclear Medicine technologist possessing the skills of handling radioactive material and calculating exact doses, no other modality can take this away from us.

As the manager of a large nuclear medicine department performing a large number of studies and procedures, what would be the ideal type of equipment that you need to satisfy the needs of your patient population?

Of course, doing therapies and imaging Y-90 is challenging. SPECT-CT is needed to help for pre-therapy planning. Utilizing functional imaging is vital for the radiologist to know if MAA is being shunted into the lungs or GI system. With body habitus providing a challenge with lower dose SPECT-CT scanners, at least a 2 slice CT scanner would be ideal. Using PET-CT with TOF, and other reconstruction methods on Y-90 scans have shown to provide more information to the oncologist. I feel each department should have 2 SPECT-CTs (depending on volume), and at the very least a PET-CT with TOF in hospitals that have a need for them. SPECT-CT provides some anatomical data that can help Nuclear Medicine compete with other modalities by having the best of both worlds.

Until a few years ago, therapy with medical isotopes was essentially driven by the treatment of thyroid cancers. Theranostics is a brand new paradigm that is invading the practice of NM. How will the clinical implementation of Theranostics change the running of nuclear medicine departments in the future?

Theranostics is the cure for what Nuclear Medicine needs. Using imaging with agents designed to attach themselves to targeted cells, this method can more effectively treat patients with often less side effects than that of chemo. Designing a Nuclear Medicine therapy clinic where Radiologist can use their skills of reading images, then planning targeted therapies can provide a great path in both Nuclear Medicine and patient care. Nuclear Medicine will need the support of their organization, with many imaging agents such as Ga-68, F-18 Axumin having an expensive upfront cost. Therapy agents are also very expensive but with support of the hospital, including reimbursement, Nuclear Medicine can thrive for all aspects of healthcare. ■

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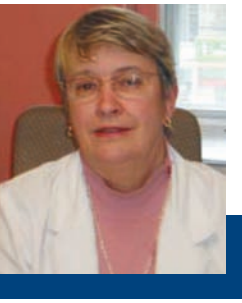
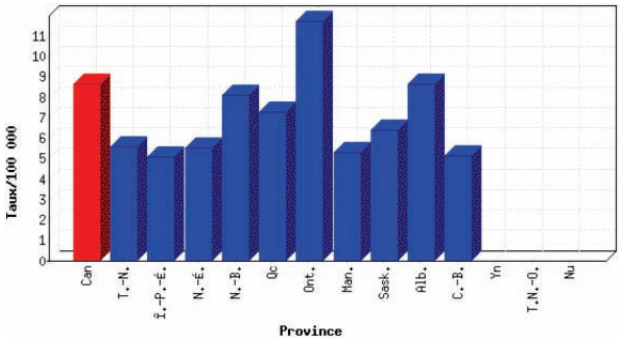


LE CANCER DE LA THYROÏDE

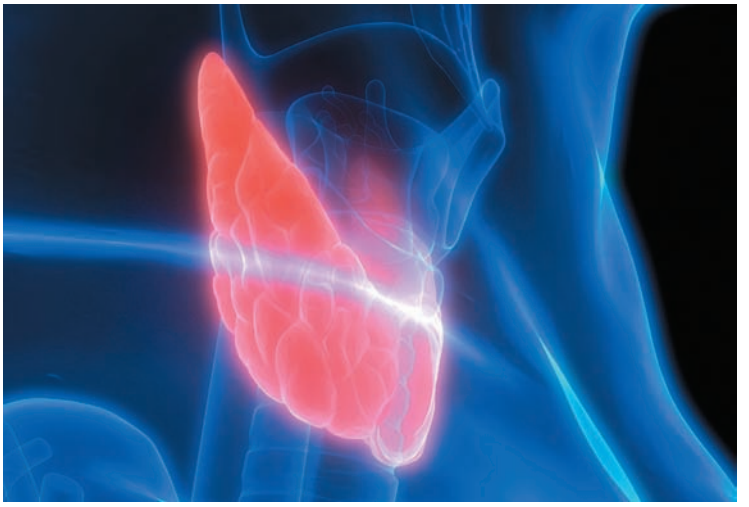
Quoique le cancer de la thyroïde ne soit pas le cancer le plus fréquent, moins de 1 % de tous les cancers, celui-ci est le plus fréquent de tous les cancers endocriniens et le plus mortel. Cependant, contrairement aux autres cancers, il est presque toujours « guérissable ». La découverte d'un nodule (masse) thyroïdien soulève la possibilité d'un cancer.

En Amérique du Nord, environ 19 500 nouveaux cas sont diagnostiqués chaque année avec 1 300 décès annuels. Cependant, 500 000 patients ont été traités efficacement et survivent. L'incidence annuelle varie entre 0,5 et 10 cas par 100 000 de population. Les statistiques canadiennes pour 2003 démontrent 8,63 cas par 100 000 habitants, soit 11 cas pour l'Ontario alors que la province de Québec est légèrement sous la limite canadienne avec 7,26 cas par 100 000 habitants.

Incidence du cancer par province/territoire
Tumeur du corps thyroïde, deux sexes combinés, tous les âges, 2003



L'incidence augmente avec l'âge chez l'adulte. L'âge moyen se situe d'une part entre 45 et 50 ans et d'autre part chez le jeune de moins de 20 ans. Le cancer est de deux à quatre fois plus fréquent



chez la femme que chez l'homme. Cependant, un nodule chez l'homme a un plus grand risque de cancer. De 5 à 36 % des adultes ont des cancers occultes à l'autopsie. Ces cancers sont petits (< 1 cm) et sont mieux reconnus et diagnostiqués actuellement grâce à une analyse microscopique sériée plus poussée.

Un registre français « Francim » actualisant les données du cancer thyroïdien notait une augmentation du cancer de 6,2 % par an chez l'homme et de 8,1 % par an chez la femme. Cette augmentation peut s'expliquer par une meilleure sensibilisation des patients, des médecins et par des moyens de détection très sensibles dont l'échographie ou la tomodensitométrie (CT-scan) à la suite d'investigation pour d'autres pathologies.

FACTEURS DE RISQUE

Le seul facteur de risque reconnu est l'irradiation à la thyroïde dans le jeune âge. Avant 1960, on irradiait à faible dose (500 – 1500 rads) diverses conditions médicales : acné, amygdalite, mycose

Incidence du cancer par province/territoire
Taux standardisé d'incidence par âge pour 100 000 habitants (Canada 1991)

	Can	T.-N.	Î.-P.-É.	N.-É.	N.-B.	Qc.	Ont.	Man.	Sask.	Alb.	C.-B.	Yn	T.N.-O.	Nu
Taux/100 000	8,63	5,55	5,09	5,52	8,07	7,26	11,70	5,26	6,36	8,62	5,12			

Infostats@statcan.ca

de la tête, thymus hypertrophique, tuberculose du cou, etc. Une période de latence de 5 ans a été observée avant l'apparition du cancer papillaire avec un pic à 20 ans et un déclin sur une période de 20 ans. L'accident de Chernobyl en 1986 a prouvé que les radioisotopes de l'iode avaient un effet cancérogène sur la thyroïde chez les enfants âgés de moins de 10 ans avec une période de latence de seulement 4 ans.

À l'âge adulte, les doses diagnostiques ou thérapeutiques d'iode et l'irradiation externe ne semblent pas majorer le risque. Cependant, toute histoire d'irradiation externe (lymphome, Hodgkin) mérite d'être surveillée et investiguée. En ce qui concerne le cancer folliculaire, celui-ci serait plus prévalent dans les régions pauvres en iode.

L'association familiale est très rare pour les cancers papillaires (« Cowden » hamartome multiple; « Gardner » : polypose familiale; aussi une forme familiale de carcinome papillaire).

Cependant, dans le cancer médullaire, il faut investiguer toute la famille avec les tests biochimiques appropriés même si l'on ne peut déceler de nodule. Le cancer médullaire est aussi associé à d'autres pathologies endocriniennes (hypophyse, parathyroïde, surrénales, pancréas). Le syndrome est appelé néoplasie endocrinienne multiple (MEN type I – II).

CLASSIFICATION

Il existe quatre types de cancer. Les plus fréquents appelés carcinomes bien différenciés (80 %-95 %) comprennent le cancer papillaire (70 % à 80 %) et le cancer folliculaire (15 % à 25 %) ou sa variante, le carcinome à cellules de Hürthle (2 % à 5 %). Ces cancers bien différenciés sont radiosensibles et sécrètent de la thyroglobuline.

Les cancers médullaires représentent 5 % des cancers thyroïdiens. Ils originent des cellules parafolliculaires ou cellules « C » et produisent la calcitonine. Le traitement est essentiellement chirurgical.

Les cancers anaplasiques ou indifférenciés sont rares (< 5 %) et sont d'une gravité extrême. Il existe enfin de très rares formes de cancers : lymphome, épithélioma malpighien, etc.

Table 1. Relative Frequencies and Mortality Rates of the Various Histological Types of Thyroid Cancer[11]

Histological Type	Relative Frequency (%)	Cause-Specific Mortality Rates at 20 Years (%)
Papillary	70 - 80	5 - 10
Follicular	15 - 25	25 - 30
Hürthle cell	2 - 5	20 - 35
Medullary	5 - 8	20 - 25
Anaplastic	4 - 10	>95

Genzyme, Europe 2005

LE DIAGNOSTIC

Tout nodule palpé n'est pas un cancer car 80 % à 95 % des nodules sont bénins. La majorité des cancers sont asymptomatiques. Certains éléments peuvent suggérer un cancer : l'âge si < 20 ans ou > 60 ans et s'il s'agit d'un homme. Lorsqu'il y a changement de la voix, dysphagie ou dyspnée, le cancer est alors très avancé.

Pour confirmer le diagnostic, l'examen le plus fiable est la cytoponction en ce qui concerne le cancer papillaire. Cependant, pour le cancer folliculaire, il faut souvent procéder à une chirurgie car les critères de malignité reposent sur l'envahissement vasculaire ou capsulaire à l'examen histologique.

La cytoponction réalisée par un spécialiste expérimenté et interprétée par un cyto-pathologiste compétent a une sensibilité de 95 % à 98 % et une spécificité de 97 % à 99 %. La cytoponction sous échographie peut amener de meilleurs résultats si la lésion est profonde ou s'il s'agit d'une lésion mixte à composante kystique. L'échographie permet aussi d'évaluer les caractères du nodule unique ou associé à d'autres nodules.

La scintigraphie thyroïdienne s'avère utile pour déterminer le statut fonctionnel d'un nodule suspect de lésion folliculaire. Seulement 5 % des nodules sont « chauds », c'est-à-dire fonctionnels et ceux-ci sont rarement malins. L'incidence de nodule fonctionnel est plus grande parmi les lésions folliculaires. Une telle trouvaille scintigraphique évite donc une chirurgie. La scintigraphie est cependant peu utile pour les nodules infracentimétriques.

Le bilan biologique devrait inclure une TSH. La calcitonine est un bon marqueur des cancers médullaires mais ne doit pas être faite de routine.

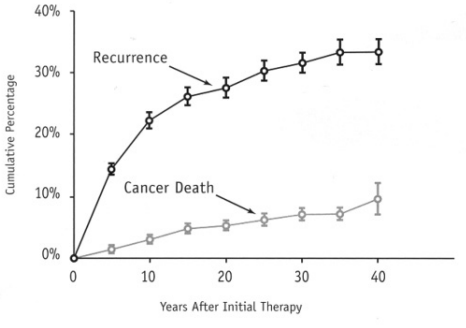
CLASSIFICATION ET STADE

Avant d'aborder le traitement, il est important de reconnaître les patients à faible risque de récidive ou de mortalité car leur traitement et leur suivi différera des patients à haut risque.

Dans le but d'uniformiser le diagnostic et l'attitude thérapeutique, le TNM a été adopté par le American Joint Committee on CANCER (AJCC) et le Tumor-Node-Metastasis (TNM) Committee of the International Union Against Cancer (UICC). Le nouveau TNM adapté tient compte de l'âge au diagnostic (l'âge <> 45 ans sert à déterminer le stade), de l'extension de la tumeur (T), de la présence de ganglions (nodes) N_1 ou N_0, et de la présence de métastases M_1 ou M_0.

Ainsi, tout patient de moins de 45 ans, sans tenir compte de T ou N, est considéré stade I s'il n'a pas de métastases à distance; avec métastases à distance, il devient un stade II. Chez les patients de plus de 45 ans, la classification est conventionnelle (TNM standard).

Figure 1. Well-differentiated Thyroid Cancer Recurrences and Deaths Due to Cancer Compared to Years After Initial Therapy[23]



Mazzaferri EL, Jhiang SM. AM J MED. 1994; 97 :418-428

Il ne faut pas oublier que même chez les patients à faible risque, il y a risque de récidive et même qu'une minorité peut en décéder.

Certains types de cancer papillaire sont plus agressifs : « tall cell », « sclérosant ». Les cancers folliculaires, surtout s'ils sont envahissants par opposition à minimalement envahissant, peuvent métastasier aux os et aux poumons. Le cancer folliculaire à cellules de Hürthle est aussi plus agressif.

LE TRAITEMENT

Nous aborderons seulement le traitement des cancers bien différenciés.

LA CHIRURGIE

La chirurgie est le traitement initial et devrait être faite par un chirurgien expert en thyroïde. Certains auteurs préconisent la lobectomie et l'isthmectomie pour les petits cancers papillaires < 1 cm de bon pronostic, mais comme les cancers papillaires sont souvent multicentriques et bilatéraux, la majorité des experts recommandent une thyroïdectomie totale ou quasi-totale, car ceci facilite le suivi et augmente la spécificité du dosage de la thyroglobuline comme marqueur du cancer dans le suivi.

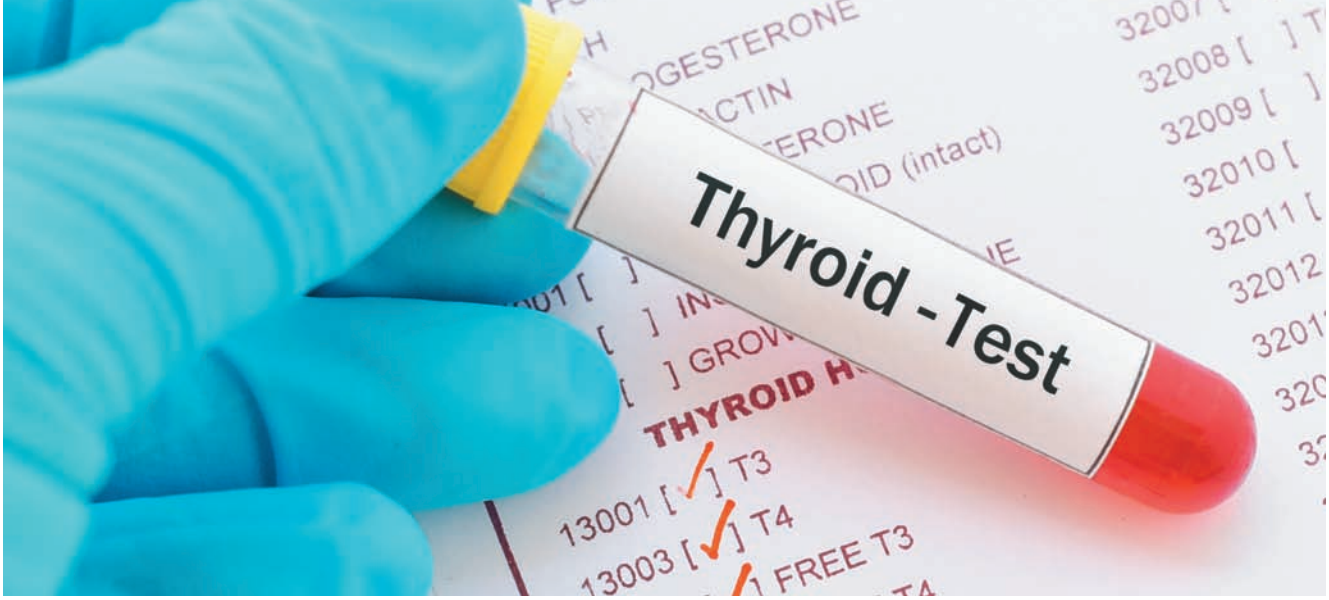
Pour les néoplasies folliculaires, on procède initialement à une lobectomie car le diagnostic ne peut être obtenu sur la base de la seule biopsie ou de la congélation puisqu'il faut démontrer l'envahissement capsulaire ou vasculaire à l'histologie. Dans la majeure partie des patients (surtout s'il s'agit d'un cancer à cellules de Hürthle), on procède à une thyroïdectomie de complétion sans risque appréciable de complications.

La dissection de routine du compartiment central (aire ganglionnaire VI) devrait être faite dans les cancers papillaires et les carcinomes à cellules de Hürthle. Dans le cancer folliculaire, la thyroïdectomie totale ou quasi-totale sans dissection ganglionnaire pourrait être appropriée.

Cependant, si des métastases ganglionnaires sont prouvées par biopsie, détectées cliniquement ou démontrées à l'imagerie, une dissection du compartiment latéral devrait être faite.

IODE RADIOACTIF

Suite à la chirurgie, un traitement ablatif à l'iode-131 est donné pour détruire le moindre tissu thyroïdien restant, les cellules cancéreuses occultes microscopiques et possiblement détruire les métastases. Pour que le traitement à l'iode radioactif soit efficace, toute hormonothérapie (T4 ou T3) doit être cessée avant le traitement, de



sorte que la TSH du patient doit s'élever à > 30 mU/l pour stimuler la captation par le tissu thyroïdien résiduel. Depuis 2002, avec l'introduction de la TSH humaine recombinante (Thyrogen), on pourrait procéder au traitement ablatif avec cette TSH exogène et ainsi éviter tous les symptômes et les complications de l'hypothyroïdie. Cette indication est approuvée en Europe mais non en Amérique du Nord. Cependant, certaines conditions médicales justifient son usage : maladies psychiatriques, patients en insuffisance rénale, maladies sévères, métastases. Après traitement à l'iode radioactif, une scintigraphie pancorporelle est réalisée 7 à 10 jours post-traitement.

TRAITEMENT HORMONAL

L'hormonothérapie (l-thyroxine) est débutée après le traitement ablatif à l'iode-131. Le but est de freiner la TSH et ainsi d'empêcher toute stimulation de tissu potentiel néoplasique. La dose utilisée de T4 est ajustée selon le poids du patient (2µgr/Kg) et dépendant du risque de récidive et de mortalité ajustée pour que la TSH soit inférieure à < 0,1 et même près de 0,01 mU/l. Pour les patients à faible risque, la TSH peut être maintenue à 0,1 - 0,4 mU/l. Il s'agit donc d'une dose de T4 supérieure à celle utilisée pour une hypothyroïdie (1,6 µgr/Kg).

SURVEILLANCE

Les cancers thyroïdiens bien différenciés démontrent une progression lente et un bon pronostic, mais il demeure nécessaire de suivre ces patients afin de détecter toute récidive (20 % à 30 %).

La thyroglobuline (Tg) (aussi la TSH) sont mesurées sous freination (l-thyroxine). La première année (6 à 12 mois) après le traitement à l'iode radioactif, on procèdera à un contrôle scintigraphique pancorporel avec dosage de la Tg sous stimulation au Thyrogen (TSH humaine recombinante). Ceci évite l'arrêt de la l-thyroxine et les effets de l'hypothyroïdie.

En plus de l'examen clinique, l'échographie cervicale (lit thyroïdien, compartiment central et latéral du cou) faite par un expert en cancer thyroïdien sert à détecter toute apparition ganglionnaire d'allure suspecte et si nécessaire, on procèdera à une cytoponction sous échographie. Ce contrôle est suggéré 6 à 12 mois après chirurgie et annuellement pour 3 à 5 ans suivant le risque du patient et le taux de la thyroglobuline.

S'il y a persistance de tissu thyroïdien avec une Tg augmentée, on peut procéder à un autre traitement à l'iode radioactif. S'il y a évidence de maladie ganglionnaire opérable, un évidement cervical doit être fait.

Si la scintigraphie pancorporelle est négative et que la thyroglobuline n'est pas augmentée, on pourrait procéder pour les 3 à 5 années suivantes au dosage de thyroglobuline régulièrement sous freination (prise de l-thyroxine et TSH freinée) et annuellement sous Thyrogen.

En présence d'une scintigraphie pancorporelle négative et d'une thyroglobuline augmentée, en plus de l'échographie, le CT-scan et même le TEP (tomographie par émission de positrons avec F^{18}-flluorodeoxyglucose) pourraient être utilisés à la recherche de métastases.

RECOMMANDATIONS

Lorsque le diagnostic de cancer est posé par cytoponction, il est nécessaire d'avoir une échographie avant la chirurgie. La présence de ganglions peut influencer l'approche chirurgicale : thyroïdectomie totale ± évidement cervical.

Dans l'investigation, si un CT-scan est absolument nécessaire, on devrait éviter l'infusion d'iode, car cet apport exogène d'iode compétitionne avec l'iode radioactif et l'on doit alors retarder le traitement à l'iode d'au moins deux mois après infusion.

De même, tout produit contenant de l'iode doit être éliminé environ 15 jours avant le traitement

à l'iode radioactif, d'où la diète sans sel (hypoiodée) qu'on recommande aux patients. Ceci inclut aussi les vitamines et tout produit naturel douteux.

Lors du dosage de la thyroglobuline, on devrait automatiquement obtenir le dosage des anticorps anti-thyroglobuline. La présence d'anticorps nuit à l'interprétation du dosage de la thyroglobuline, mais est un signe indirect de la présence de celle-ci. De même, pour la fiabilité et la reproductibilité des résultats, le dosage devrait toujours être fait dans le même laboratoire. Ce dosage n'est cependant jamais nécessaire avant l'opération (puisqu'il y a du tissu résiduel).

Lorsque l'on doit retarder le traitement à l'iode radioactif plus de 4 à 6 semaines après l'opération, le patient peut recevoir de la l-thyroxine ou de préférence du Cytomel (T3) car la demi-vie de celui-ci est plus courte (1-2 jours/7 jours).

Dans la surveillance des patients, le médecin de famille ne devrait pas se surprendre si le patient est en hyperthyroïdie car dépendant de la gravité du cancer, on veut une suppression totale de la TSH pour éviter toute stimulation sur les cellules cancéreuses. Chez certains patients symptomatiques (tachycardie, insomnie, risque d'ostéoporose) et évoluant bien, la dose de Synthroid pourrait être réduite. Mais avant de penser à réduire la dose de l-thyroxine, on conseille de communiquer avec le spécialiste qui assure le suivi du patient.

PRÉVENTION ET DÉPISTAGE

L'histoire médicale et l'examen clinique demeurent l'approche conventionnelle. La mesure de la TSH évalue la fonction thyroïdienne. L'échographie cervicale et la scintigraphie thyroïdienne doivent être utilisées à bon escient. La tomodensitométrie (CT-scan) ne devrait pas être utilisée de routine à moins de symptômes compressifs.

COLLABORATION MÉDECIN-PHARMACIEN

Le Cytomel (triiodothyronine) est parfois prescrit pour de courte durée avant un examen ou un traitement à l'iode radioactif pour diminuer les symptômes d'hypothyroïdie après chirurgie ou arrêt de la l-thyroxine pour un mois. L'arrêt du cytomel pendant 15 jours suffit à entraîner une augmentation de la TSH.

La l-thyroxine chez les patients avec un cancer thyroïdien est prescrite suivant le poids et aussi dans le but de supprimer la TSH. La dose est donc plus grande (2 µg/kilo) que chez un simple hypothyroïdien (1.6 µg/kilo).

Suite à une thyroïdectomie totale, le patient peut occasionnellement, pour une certaine période, présenter une hypocalcémie. Le calcium ne devrait pas être ingéré concomitamment à la l-thyroxine (Synthroid, Eltroxin) car ce dernier sera mal absorbé. Le clinicien se verrait obligé d'augmenter la dose alors qu'un horaire différent dans la prise des médicaments règlera facilement le problème.

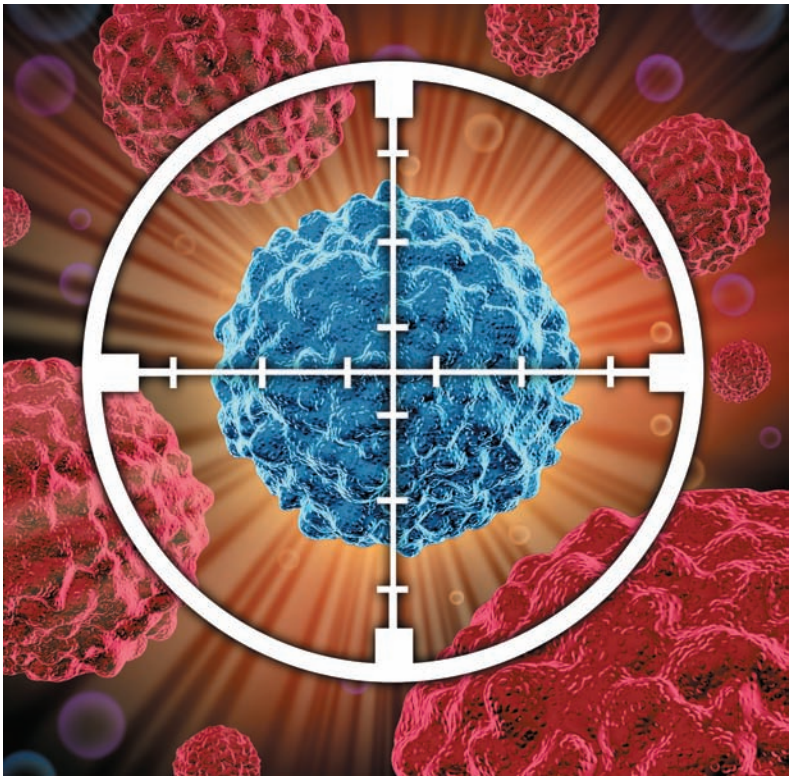
TABLEAU RÉCAPULATIF

L'incidence plus grande de cancers thyroïdiens, surtout papillaires, est en partie attribuable à la découverte fortuite et précoce de nodules thyroïdiens lors d'échographie cervicale ou lors d'un examen radiologique (radiographie pulmonaire, tomodensitométrie).

En soi, les cancers thyroïdiens évoluent lentement, de façon indolente, présentent peu de morbidité et de mortalité et un haut taux de guérison. Cependant, ces cancers peuvent récidiver et certains cancers ont un caractère plus agressif.

Il est important de bien identifier les patients à faible risque et à haut risque en tenant compte de l'âge, du sexe, des caractéristiques de la tumeur (sous-types histologiques), de son extension et de la présence de métastases (ganglionnaires ou autres) au moment du diagnostic.

La surveillance est donc importante initialement et à long terme. La mesure de la thyroglobuline sous freination et sous Thyrogen, combinée avec une échographie cervicale de qualité, fournit les meilleurs indices de maladie résiduelle ou récidivante. ■



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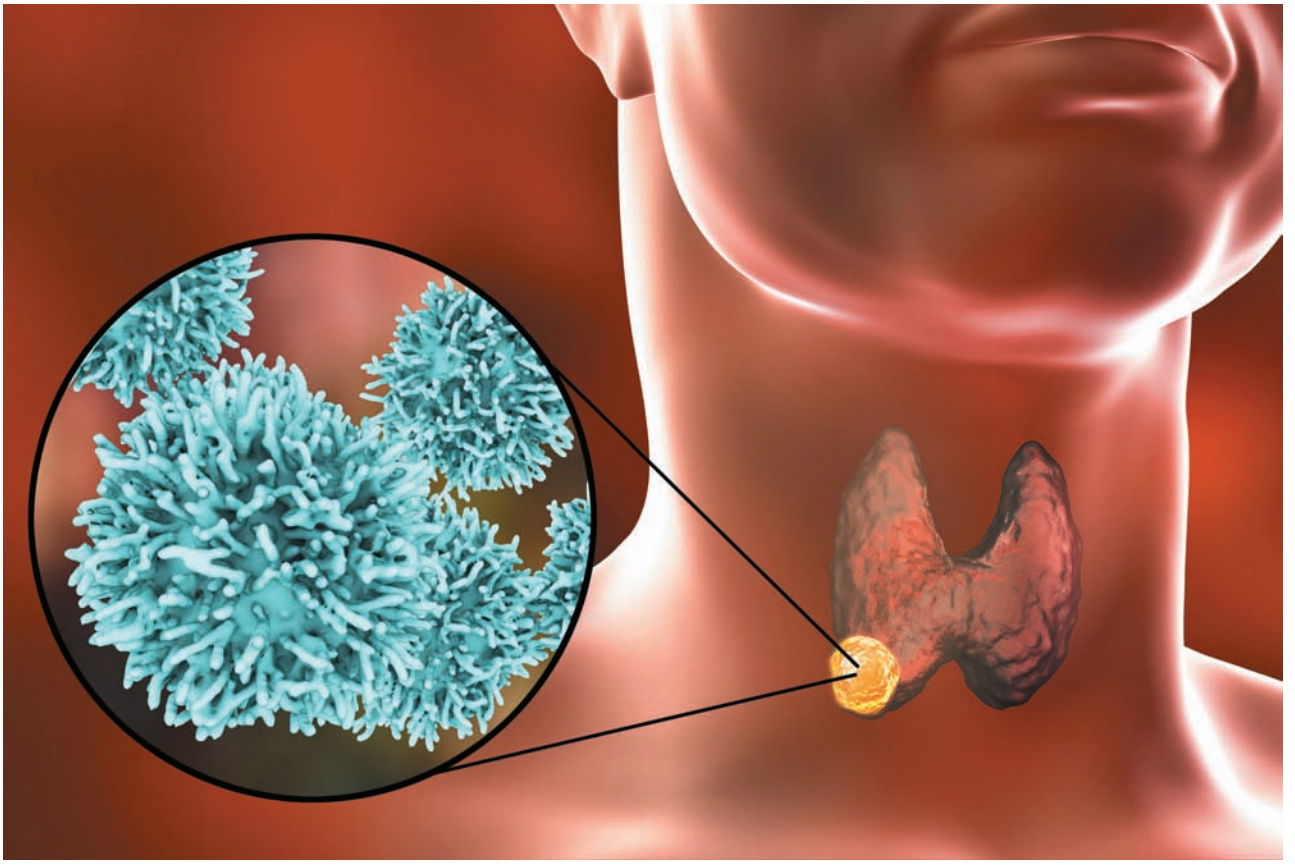
Medicina Nuclear y Cáncer de Tiroides: Situación Actual

Cada vez es más común tener un familiar o conocido que se haya realizado una cirugía tiroidea por un cáncer. Si bien esta percepción es correcta, se están operando más pacientes de tiroides en relación a otros cánceres proporcionalmente, la gravedad de esta "epidemia" no es tal. La letalidad del cáncer de tiroides no ha cambiado respecto a los datos históricos, y sigue siendo considerado un "buen cáncer", con tasas de curación superiores al 95%.

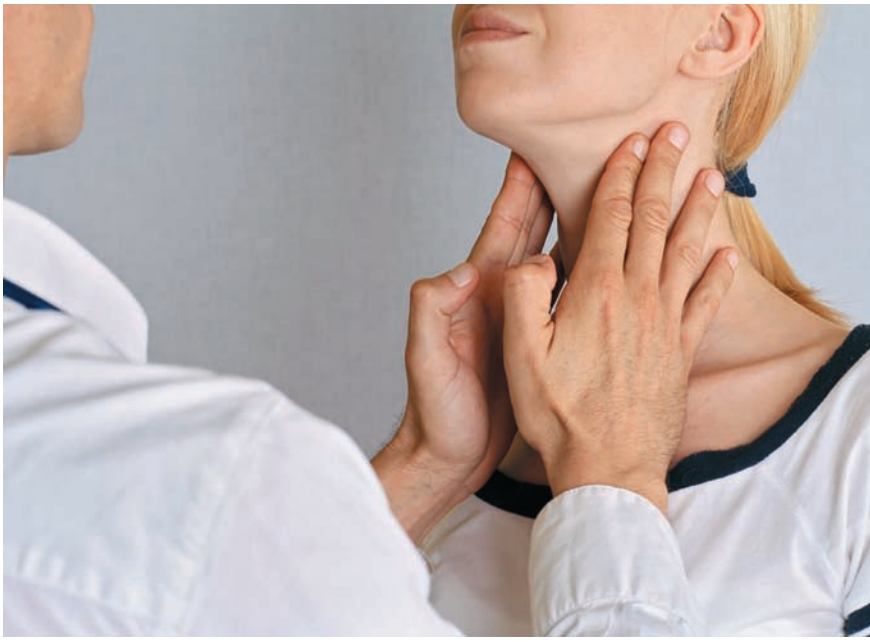
Entonces, ¿por qué han aumentado las tasas de incidencia del cáncer de tiroides? La respuesta es relativamente sencilla, y consta de dos razones principalmente. La primera es la mayor pesquisa de enfermedades tiroideas, no necesariamente cáncer, principalmente gracias a estudios rutinarios de laboratorio de hormonas tiroideas que son solicitados por médicos generales y especialistas diversos como endocrinólogos, ginecólogos, geriatras, cardiólogos y muchos otros. Esto se puede dar en el contexto de controles rutinarios en el embarazo como en estudios por sobrepeso u obesidad o hasta en estudio de sintomatología inespecífica como el cansancio o "falta de ánimo". Si estos exámenes salen alterados, el siguiente paso generalmente implica un estudio de imágenes dirigido, como la ecografía, que nos lleva a la segunda razón de la mayor incidencia del cáncer tiroideo: La notable mejoría en los últimos años de la capacidad imagenológica para identificar adecuadamente nódulos tiroideos. Si bien la principal herramienta para identificar y evaluar los



nódulos es la ecografía, la proliferación de otras técnicas como la Tomografía Computada (TC), Resonancia Magnética (RM) e incluso la Tomografía por Emisión de Positrones (PET) permite la identificación incidental de nódulos tiroideos con bastante frecuencia, lo que motiva su estudio dirigido.

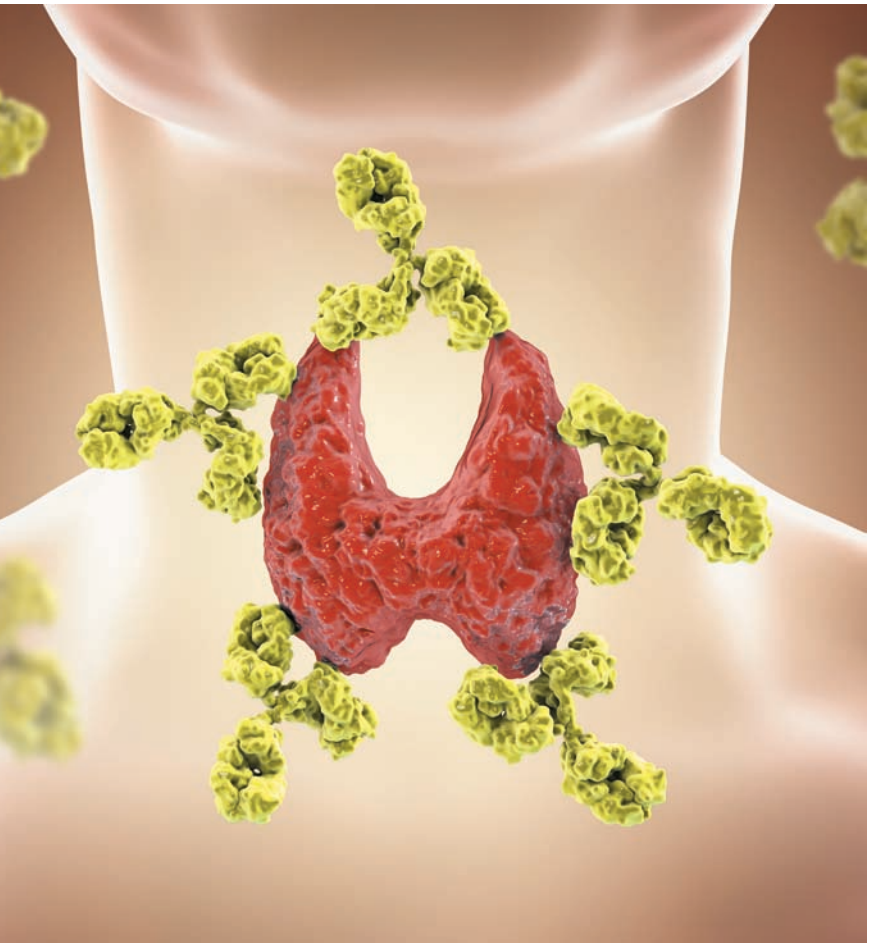
Se estima que hasta dos tercios de la población adulta puede presentar nódulos tiroideos, con una mayor frecuencia a medida que se envejece. La enorme mayoría de estos nódulos corresponde a lesiones benignas, pero se estima que entre el 5 y 10% de ellos efectivamente corresponde a lesiones cancerosas. Por muchos años se enfatizó en el estudio de los nódulos tiroideos mediante imágenes y posterior punción con aguja fina para obtener muestras que permitieran un diagnóstico histopatológico, lo que derivó en el diagnóstico de una gran cantidad de lesiones cancerosas. La resección quirúrgica completa de la glándula es la primera opción de tratamiento en estos casos, complementando posteriormente la terapia con una dosis de radioyodo para destruir el tejido tiroideo remanente.

El rol de la medicina nuclear en el tratamiento complementario de los pacientes con cáncer de tiroides se remonta a los inicios de la especialidad, en la década de 1940, cuando se demostró la utilidad del radioyodo en pacientes con metástasis de cáncer de tiroides. El concepto fisiológico es sencillo, las células tiroideas utilizan el yodo para fabricar hormona tiroidea, por lo que al administrar un isótopo radioactivo del yodo con energía Beta como el I-131 se logra una radiotoxicidad que termina destruyendo las células. El yodo que no ingresa a las células es eliminado por las secreciones corporales, principalmente orina, evitando dañar significativamente otros tejidos. El cáncer de tiroides puede ser de varios tipos, la gran mayoría mantiene la capacidad celular de producir hormona tiroidea, por los que se les agrupa como Cáncer Diferenciado de Tiroides (CDT), lo que los hace susceptibles a la terapia con radioyodo. La posibilidad de destruir las células tiroideas que quedaron como remanente en el lecho quirúrgico permitió además mejorar el seguimiento a largo plazo de estos pacientes, ya que da la posibilidad de realizar una medición de la Tiroglobulina circulante en sangre (Tg) para evaluar posibles recurrencias. Al destruir la fuente productora de Tg, ésta debiera descender a niveles muy bajos o indetectables, por lo que un alza durante el seguimiento, por leve que sea, indicaría que está aumentando la masa de células productoras y deberá hacer descartar presencia de una recurrencia del tumor. La capacidad de destruir las eventuales metástasis del CDT en ganglios linfáticos, pulmón, huesos u otras ubicaciones, generalmente con una dosis mayor de radioyodo, permitió además enfrentar con



bastante éxito los casos de CDT avanzados. Por años se empleó una dosis relativamente fija de radioyodo para tratar los CDT confinados a la tiroides, con una dosis algo mayor si se demostraba compromiso ganglionar y otra dosis mayor si había compromiso metastásico a distancia. El I-131 además de entregar parte de su energía en forma de partícula Beta, con el efecto terapéutico descrito, emite un fotón gamma que capaz de ser captado por los equipos de Medicina Nuclear. Esto permite obtener imágenes que demuestran la distribución corporal del radioyodo, estudio que se realiza rutinariamente luego de las terapias para confirmar la concentración a nivel del remanente tiroideo y también para confirmar o descartar presencia de metástasis del CDT. Al ser una terapia dirigida, con buenos resultados, de relativa baja toxicidad y bien tolerada, el tratamiento con radioyodo se alzó indiscutidamente como el complemento ideal a la cirugía en el tratamiento del CDT.

El cambio de tendencia hacia una medicina más personalizada en los últimos años versus el concepto más generalizado empleado anteriormente hizo que se estudiara mejor al grupo de pacientes con cáncer de tiroides. La Sociedad Americana de Tiroides (ATA) publicó recientemente una serie de recomendaciones clínicas para clasificar el riesgo de los pacientes con cáncer de tiroides. Esta clasificación parte en aquellos con un riesgo muy bajo de tener recurrencias o futuras complicaciones por su cáncer y termina definiendo aquellos que presentan un alto riesgo de presentar enfermedad recurrente, pasando por las categorías intermedias de riesgo. Existen diferentes variables que se deben tomar en consideración para clasificar adecuadamente a cada paciente en una categoría de riesgo, entre



ellas destaca el tamaño y número de lesiones, el tipo histológico del cáncer, la presencia de factores sugerentes de mayor agresividad como compromiso de la cápsula tiroidea o extratiroideo, presencia y magnitud de la invasión vascular, número y tipo del compromiso ganglionar en caso de existir, e incluso considera presencia de mutaciones genéticas del paciente. Esta clasificación de riesgo se basa en la experiencia acumulada de los últimos decenios y pretende ser una guía para ayudar a los médicos a indicar el tratamiento complementario a la cirugía.

La evidencia disponible a la fecha sugiere que en la gran mayoría de los casos catalogados como de bajo riesgo bastaría solamente con el tratamiento quirúrgico para controlar la enfermedad, sin ser necesario dar radioyodo complementario. De hecho, la mayoría de las recomendaciones actuales no indican estudiar con biopsia aquellos nódulos pequeños (menores a un centímetro) aunque existan algunos indicadores que hagan sospechar la presencia de cáncer. Los pacientes catalogados de riesgo intermedio pueden tener indicación de terapia complementaria con radioyodo en algunos casos, debiendo discutir las diferentes opciones con su equipo de médicos tratantes para evaluar las ventajas y potenciales desventajas caso a caso. Aquellos pacientes de alto riesgo deben necesariamente recibir terapia complementaria con radioyodo, para tratar de disminuir al máximo la posibilidad de la recurrencia de la enfermedad.

Junto con el cambio en el manejo pre y post quirúrgico de estos pacientes, en los últimos años también se diseñaron y llevaron a cabo estudios que apuntaron a evaluar la efectividad de dosis menores de radioyodo para lograr el efecto requerido de eliminar el tejido tiroideo residual post quirúrgico. Históricamente se administraba una dosis de 100 miliCuries (mCi) en la gran mayoría de las terapias, elevándose a más del doble en algunos casos con metástasis a distancia. Los resultados de los nuevos estudios permiten que actualmente se pueda administrar dosis bastante menores, desde 30mCi, que se indican generalmente en aquellos pacientes de menor riesgo. Se siguen reservando las dosis de 100mCi o más en aquellos pacientes de riesgo alto, o con metástasis conocidas, ya que se apunta a maximizar el efecto terapéutico. La ventaja de disminuir las dosis en estos pacientes es que podemos efectivamente reducir el riesgo de complicaciones asociadas al radioyodo, manteniendo la efectividad de la terapia. Las complicaciones secundarias a la administración del radioyodo son en gran medida directamente dependientes de la dosis administrada y/o acumulada, dividiéndose entre efectos agudos y los de aparición tardía. Entre los efectos agudos se encuentran principalmente las molestias gastrointestinales (náuseas, vómitos, inapetencia) así como la inflamación temporal de las glándulas salivales mayores. Los efectos a largo plazo pueden incluir la disminución de la producción de saliva, secundaria a la atrofia de las glándulas salivales, y la posible aparición de lesiones tumorales secundarias a la radiación, predominantemente en sistema urinario y digestivo. Si bien la mayoría de estos efectos son controlados medicamente (los agudos) o minimizado su riesgo (los a largo plazo) y no tienen una alta tasa de ocurrencia en la mayoría de los pacientes que reciben una dosis única de radioyodo, el hecho de disminuir la carga de radiación es una clara ventaja respecto a los protocolos de terapia utilizados antiguamente.

En resumen, durante los últimos años se ha modificado significativamente el manejo de los pacientes con CDT: muchos de ellos evitan cirugías realizando un seguimiento ecográfico de sus nódulos; mientras que los pacientes operados se catalogan según riesgo para evaluar la necesidad de terapia complementaria con radioyodo. Las terapias con radioyodo siguen siendo un pilar en el tratamiento del CDT, pero al adoptar la nueva política de reducción de dosis, menos pacientes presentarán efectos secundarios indeseados y las terapias serán mejor toleradas. ■

Interview with: Dr. Danfer Huapaya
President, ALASBIMN

This past November ALASBIMN has held a very successful scientific meeting in Santiago de Chile. You are now the new President of ALASBIMN. Can you give the international readers of the magazine an overview of the efforts of ALASBIMN to promote Nuclear Medicine in Central and South-America?

The Latin American Association of Societies of Biology and Nuclear Medicine (ALASBIMN) has been supporting the different Nuclear Medicine Associations in our region, trying to make strategic alliances with the different international scientific Societies such as the American Society of Nuclear Cardiology (ASNC) and the IAEA in order to improve the training and learning of nuclear physicians in our region. It also encourages us to research and publish our research papers in the ALASBIMN journal, which helps its dissemination at the regional level. However, we still need to consolidate much more all the associations of Central and South America in order to support each other.

You are very familiar with the strengths and needs of the Peruvian Health Care system. Can you give us an idea of the assets and challenges of the practice of NM in Peru?

Peru is a country of a diverse geography and therefore our resources in the field of health are still scarce giving priority to comprehensive basic health. However, in the last ten years we have significantly improved our technology in the field of imaging. Nuclear medicine has developed a lot in the capital, with 15 nuclear medicine centers and only 3 nuclear medicine centers in some provinces of the north and south of the country with SPECT, SPECT / CT and three PET-CT scanners that are only located in the capital of the country. Our challenge is to spread even more our nuclear medicine specialty throughout the country and have a greater number of gamma cameras in those places where there is no specialty and generate more jobs for young nuclear physicians who have just graduated from the specialty. Also, one of our limitations is that we do not have many suppliers of radioactive products nationwide and we have limitations with several radiopharmaceuticals, especially in the field of PET-CT.

You have had the opportunity to read the first issue of the NM magazine Pangea-ePatient. What do you think of the magazine and what would your suggestions be to improve it?

I had the opportunity to read the first issue of the journal at the ALASBIMN congress in Santiago de Chile in November 2017 and it seemed like a very educational magazine that promotes different articles and works of the different specialists in nuclear medicine. It would be great to have the Pangea-ePatient magazine in the future through an internet platform and be able to have access in the different countries of Central and South America.

Where will the 2020 ALASBIMN meeting be held?

It will take place in Lima – Peru from November 13 to 16, 2019.

Dr. Batool Al Balooshi, MD, Facharzt, FEBNM
Consultant and head of Dubai Nuclear Medicine and Molecular Imaging center
Dubai Hospital- Dubai Health Authority

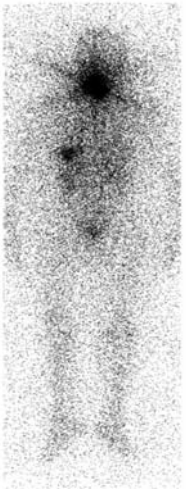
Basic approach to Radioiodine (I-131) Therapy for Differentiated Thyroid Cancer

The differentiated thyroid cancer (DTC) is the most frequent endocrine cancer in the adult population. It represents about 1% of all malignant tumors and it is more frequent in women than in men.

The vast majority of DTC have a good prognosis and the patients affected have a long survival rate. The management of DTC requires a continuum of care involving diagnosis, treatment, follow up and the assessment of remission. While practice vary from one region to another, these tasks are best performed by a multidisciplinary team that include family medicine physicians, endocrinologists, surgeons, and nuclear medicine specialists.

Surgical resection of the unilateral or bilateral thyroid cancer is the first step in management of patients who are usually diagnosed by sonography or thyroid scintigraphy performed because of difficulty of swallowing, the feeling of a lump in the throat, or simply after the incidental finding of a nodule during a routine physicial examination. The final diagnosis of thyroid cancer is established by histopathological sampling and analysis using fine needle aspiration biopsy or frozen section during the main thyroid operation.

After surgery, patients are referred either by surgeons or endocrinologists to Nuclear Medicine specialists for whole body ablation with radioiodine (I-131). Ablation refers to the first dose of radioiodine usually used to destroy the eventual remnant thyroid tissue after surgery. Further doses and therapies are referred to as repeat-ablation. All patients after surgery must achieve a true or virtual hypothyroid state in order to benefit from radioiodine treatment. Therefore ablation or re-ablation is performed through endogenous TSH stimulation (no thyroid medicationfor 4 weeks after thyroidectomy or exogenous TSH stimulation (using 2 rTSH intramuscular thyrogen injection). TSH at the time of ablation must be at least over 30-40 ul/UL. Prior to ablation, an evaluation of residual thyroid tissue is done by means of a low dose whole body radioiodine 131 diagnostic scan or in some instances with a pertechnetate thyroid scintigraphy. With a minimal amount of residual/remnant thyroid tissue a radioiodine ablation can be planned. Seven to 10 days prior to radio-iodine therapy, patients are requested to follow a low iodine diet and to avoid imaging with iodine containing contrast media like the ones used for CT studies.



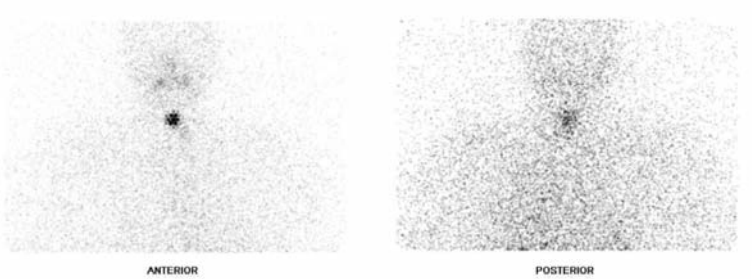
Whole body ablation radioiodine 3700 Mbq (I-131)

Patients are usually admitted to the hospital/ medical center for the oral administration of their radio-iodine therapy. They are eventually premeditated with an antiemetic such as metoclopramide 30 minutes prior to the radioiodine capsule administration to avoid nausea and to accelerate the radioiodine capsule from the stomach into the intestines. Patients are usually allowed to eat 1 hour after therapy. The duration of stay in hospital is subjected to radiation protection rules and regulations in each country; patients can start their thyroid hormone replacement therapy 48 hours after ablation.

A iodine 131 whole body scan is performed 7 days after therapy to assess the distribution of iodine 131 within the body with particular attention to the thyroid bed and possible metastatic lesions.

A control diagnostic fwhole body scan with lanother ow dose of radioiodine I-131 is performed 6 months after therapy to evaluate treatment response and the eventual need for re-ablation.

Pregnacy is an absolute contraindication for radioiodine therapy. Pregnancy or fathering after radioiodine therapy must be avoided 6-12 months.



Diagnostic radioiosine scan 185 MBq (I131)

Wei He,
M.D., PH. D.,
Director of nuclear medicine departement and PET/CT
Center Fu Dan University, affiliated with Shanghai
Hua Dong Hospital
China

甲状腺癌

甲状腺癌是内分泌系统和头颈部肿瘤中最常见的恶性肿瘤，其主要病理分型分为乳头状癌和滤泡状癌。近30年，除非洲地区因疾病诊断技术受限之外，世界大多数地区甲状腺癌发病率呈持续上升趋势。2016年，全球甲状腺癌新发病例数约为298 000例，死亡例数40 000例，虽有37%的新发病例来自欧美地区，但死亡主要发生在亚洲。我国甲状腺癌新发病例数占全球新发病例数的15.6%，死亡数占13.8%。2016中国肿瘤登记数据显示，2015年全国甲状腺癌发病率为4.12/10万，男性1.93/10万，女性6.42/10万；同期全国甲状腺癌死亡率为0.34/10万，男性0.23/10万，0.46/10万。近20年，我国甲状腺癌发病率一直呈上升趋势。中国肿瘤登记数据显示，2003-2012年甲状腺癌发病率逐年上升，死亡率较为稳定。

甲状腺癌大体分为分化型与未分化型，乳头状癌属分化型。分化型具有摄碘131功能，因此临床上用来治疗分化型甲状腺癌，特别是血行转移灶（肺、骨）。

碘-131治疗分化型甲状腺癌的指征推荐：
1、已知存在肺、骨等脏器的远处转移（M1），高危，强烈推荐进行碘-131治疗（提高疾病特异性生存率和无病生存率）；

2、术中肉眼可见肿瘤突破甲状腺包膜并侵犯皮下软组织、喉、气管、食管、喉返神经、椎前筋膜或包绕颈动脉和纵膈血管（无论肿瘤大小，T4），手术切除不完全，远处转移，高TG血症，个数不限但最大径大于或等于3厘米病理阳性的颈部淋巴结转移瘤，滤泡型甲状腺癌伴广泛血管侵犯（血管侵犯超过4处）。具备上述之一者即为高危，均强烈推荐进行碘-131治疗（提高疾病特异性生存率和无病生存率）；

3、原发肿瘤直径超过4厘米或镜下外侵（T3）、颈部淋巴结转移（N1），中危，应根据年龄、肿瘤外侵范围、淋巴结转移瘤数量和大小等选择性进行碘-131治疗；

4、虽然肿瘤没有突破甲状腺包膜且直径介于1—4厘米（T1b-2），低危，通常不建议行碘-131治疗，但若手术病理提示侵袭性组织学表现（如高细胞、柱状细胞、钉状细胞癌等）则可考虑进行碘-131治疗。

5、无外侵和转移的微灶癌（直径小于1厘米），无论单发还是多发病灶都应视为低危，不常规建议行碘-131治疗，除非有复发风险调整、疾病随访、患者意愿方面的考虑。

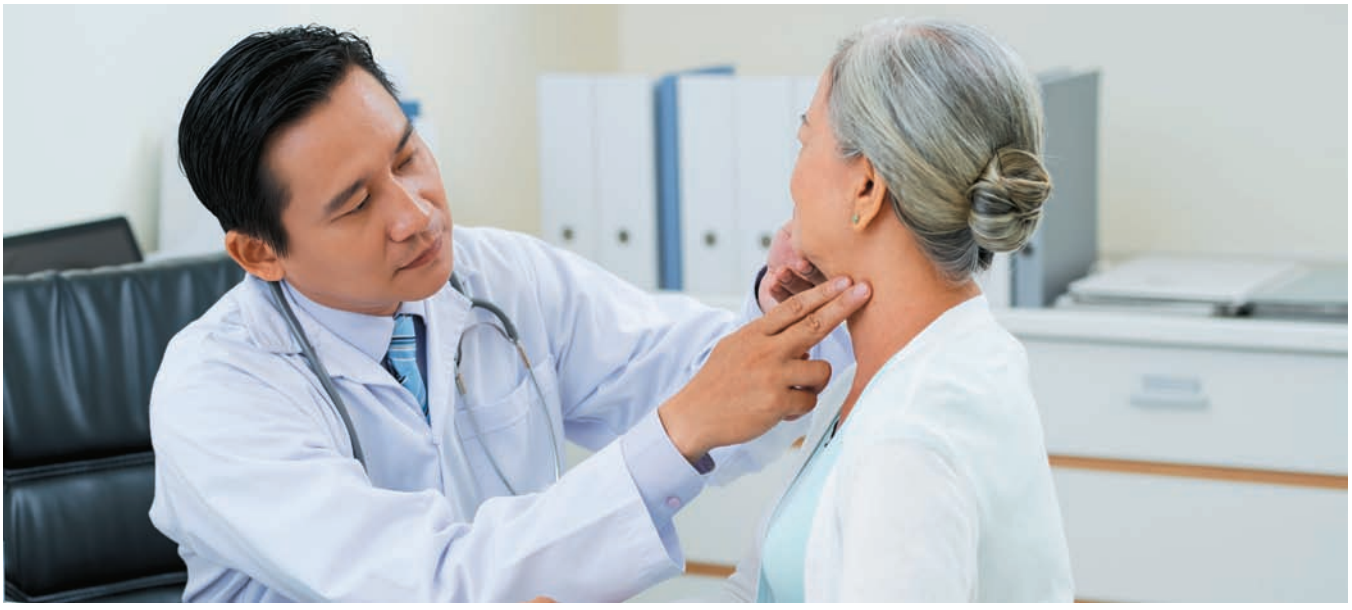
碘-131治疗分化型甲状腺癌的方法分类

严格来讲，广义的甲状腺癌术后碘-131治疗从实际方法和目的上可细分为三种具体情形，即残甲消融、碘-131辅助治疗和甲状腺癌碘-131治疗。

残甲消融，俗称“碘-131清甲”，是指通过口服碘-131的方法，使（术后残留）正常甲状腺组织受到靶向性电离辐射作用而坏死，充分实现甲状腺组织的去功能化。其作用在于降低术后甲状腺癌的复发、死亡风险并有利于进行疾病分期和随访（监测血清甲状腺球蛋白TG）。应该视残留甲状腺的大小和摄碘能力进行碘-131使用剂量决策，通常使用的碘-131剂量（活度）范围为30-150毫居里。

狭义的“甲状腺癌碘-131治疗”是指是指通过口服碘-131的方法，使甲状腺癌残留、复发、转移灶受到靶向性电离辐射作用而坏死，起到抑制甚至治愈甲状腺癌的作用。通常使用的碘-131剂量（活度）范围为150-250毫居里。

当然，在具体临床实践过程中，特别是首次收治时，部分患者同时存在残甲和潜在转移灶（或复发、残留）的可能。为了最大限度提高疗效、减少疗程数并降低辐射损害和医疗开支，在条件允许的情况下，可以使用碘-131治疗以同时起到残甲消融和辅助治疗甲状腺癌病灶的双重作用，此时就难以严格区分“消融”和“治疗”了，或者说两种情况可以同时进行，称为碘-131辅助治疗，通常使用的碘-131剂量（活度）范围为150-200毫居里。



Dr. François Lamoureux,
M.D.,M.Sc., FRCP(C),
President-elect CANM, Canada

LE CERVEAU, LA MERVEILLE DE L'ÊTRE HUMAIN

Le cerveau de l'être humain demeure une grande énigme. Comment cette structure arrive-t-elle à gérer l'ensemble de l'activité de l'Homme? D'abord elle est le siège de la perception de tous les sens. En effet, on voit par les yeux mais on perçoit les formes et les couleurs par le cerveau. Il en est de même pour l'audition : les vibrations sonores sont véhiculées par l'ensemble des structures de l'oreille, mais le décodage de ces vibrations s'effectue à l'intérieur du cerveau. La motricité ne peut s'effectuer sans l'apport du cerveau dont le siège se situe dans le lobe temporal où l'on retrouve l'homunculus, une copie virtuelle d'un être humain renversé.

Pour des mouvements, des perceptions, des pensées ou des émotions, tout origine ou requiert l'apport du cerveau.

Le cerveau est également le siège de la mémoire. Dès le début de la naissance et tout au long de la vie, tout est enregistré à tout jamais comme dans des petits tiroirs. Les enfants sont de vraies éponges et ils gobent facilement d'énormes quantités d'informations. Par exemple, les enfants peuvent reconnaître beaucoup plus d'odeurs que les personnes âgées.

Certaines maladies en fin d'âge peuvent amener une perte des éléments récents et réactiver le souvenir de faits anciens.

MAIS COMMENT EST-CE POSSIBLE?

Principalement parce que le cerveau possède un arsenal extrêmement complexe et sophistiqué de structures mues par des échanges chimiques et

activées par l'équivalent d'une puissante centrale électrique. En effet, continuellement, jour et nuit voyagent dans le cerveau comme transmetteurs des courants électriques et des molécules chimiques.

Le cerveau est superbement protégé par une composante liquidienne, mais également par deux autres composantes protectrices, les méninges, et le tout dans une boîte osseuse, la voûte crânienne.

Il existe tout un réseau de canaux liquidiens, soit la circulation sanguine cérébrale et la circulation céphalo-rachidienne. Quant aux cellules, elles se comptent par dizaines et des dizaines de milliards.

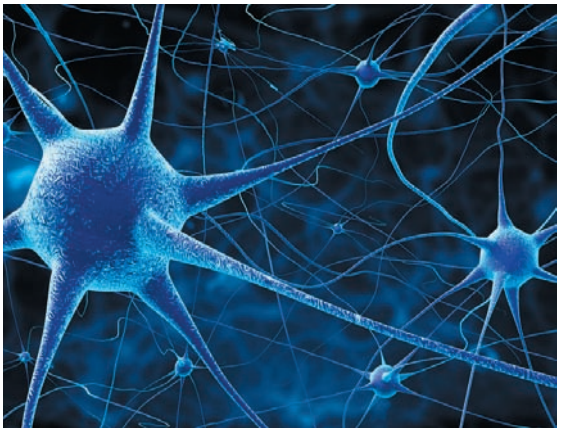
Cette structure de l'être humain est d'une complexité incroyable et c'est pourquoi, aussi, on a des experts médecins comme des neurologues, des neurochirurgiens ou des psychiatres, des pharmaciens, des psychologues et autres qui ont une grande connaissance et expertise des problèmes qui peuvent surgir dans cet incroyable univers.

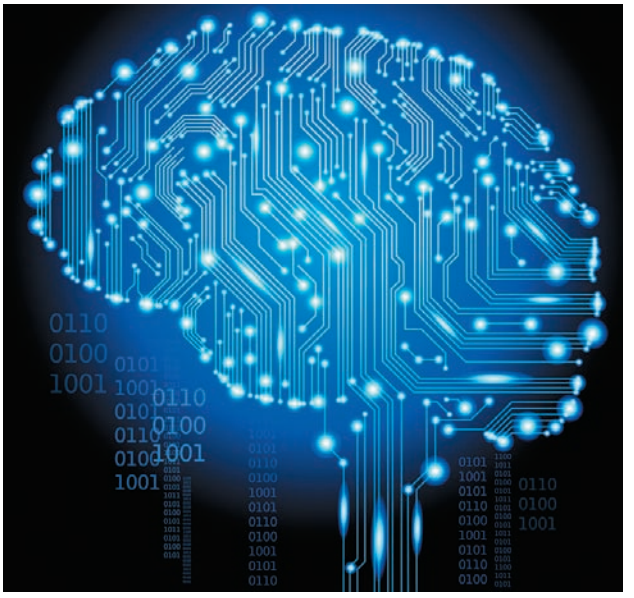
Quelle merveille que ce cerveau! Jusqu'à maintenant ces richesses sont uniques et propres à chaque être humain et on ne peut en partager l'acquis en partie ou en totalité.

Mais peut-être qu'un jour? ■

NUCLEAR IMAGING OF THE BRAIN

The microcomputer revolution of the 20th century has forever changed the way we live and interact with our world and the universe. Desktop, laptops, smartphone and tablets have empowered human beings and unleashed their creative potentials to unimaginable levels. Essentially based on sophisticated computing, artificially intelligent and self-taught machines



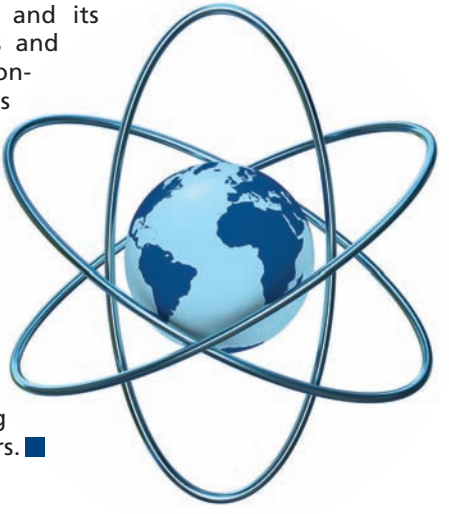


are now on the verge of another major revolution: the robots' revolution.

While the artificial intelligence machines that we design can help us better understand how the human brain learns and functions, we are far away from unravelling the fundamental secrets of the millions years old human natural intelligence.

CT scanners and MRI machines can provide minutes detail of the anatomy of normal and diseased brains. Functional MRI sheds light on the activity of the various parts of the brain. Molecular Imaging enables the characterization and the quantitation of the molecular processes that sustain the brain structure and function in normal and diseased states.

The unique ability of nuclear medicine to trace and quantify the distribution of minutes amounts of peptides, hormones, transmitters and organic molecules that are the very basis of the fundamental molecular mechanisms of the functioning of the brain and its disturbancies has been, is and will be the golden non-invasive tool to unravel its secrets.



In this and the upcoming issues of Pangea-ePatient you will find information and articles that detail the safe and useful use of medical isotopes and radiopharmaceuticals that are available to help diagnosing and managing patients with brain disorders. ■

Daniel G. Amen, MD
Founder, Amen Clinics
Costa Mesa, Los Angeles, and Walnut Creek, CA
Seattle, Atlanta, DC, NYC, Chicago

INTERVIEW WITH DR. DAN AMEN

Over the last 30 years, you have developed and relied on brain SPECT imaging to diagnose and manage all kinds of neuro-psychiatric disorders. Why is brain SPECT an essential part of your practice?

When I was a young US Army soldier, I was trained as an x-ray technician. As our professors used to say, "How do you know unless you look?". During medical school, someone I loved tried to kill herself and I took her to see a wonderful psychiatrist. I came to realize that if he helped her, which he did, it wouldn't just help her. It would help her children and even grandchildren. I fell in love with psychiatry because I realized it had the potential to change generations of people; but psychiatry is the only medical specialty that virtually never looks at the organ it treats. SPECT completely changed the paradigm and gave us an elegant way to look at brain function. It has taught us many important lessons, such as all psychiatric illnesses are not single or simple disorders. ADHD, depression, bipolar disorder, violence, etc., all have multiple types that each require their own treatments. This completely changed how we treat patients. In addition, we learned that mild-to-moderate traumatic brain injuries ruin people's lives and few professionals know it, because they never look at brain function. The most exciting lesson we have learned with SPECT is that you are not stuck with the brain you have, you can make it better and we can prove it.

You have been a very vocal advocate of brain health. What is brain health? In the era of Alzheimer's disease, TBI and PTSD, how can people develop, maintain or regain a healthy brain?

Funny, but being a physician and double board-certified psychiatrist, until I started to look at the brain with SPECT, I never really cared about my own brain. After having scanned tens of thousands of people, and myself and family, I came to realize that success starts in the physical well-being of the brain. When your brain works right, you work right; and when your brain is troubled for whatever reason, you are much more likely to have trouble in your life. Over the years I have been able to simplify brain health into three categories: brain envy (you must care about it); avoid things that hurt it; and engage in regular brain healthy habits. My book *Memory Rescue* was just published. In it I argue that if you want to prevent Alzheimer's Disease and cognitive decline with age, you must prevent or treat the 11 major risk factors that steal your mind. And the good news is that nearly all the risk factors are either preventable or treatable. My team and I developed the mnemonic BRIGHT MINDS to help people remember these risk factors: Blood flow, Retirement/aging, Genetics, Head trauma, Toxins, Mental health issues, Immunity/Infections, Neurohormone deficiencies, Obesity and Sleep. If you love yourself, doing the right things for the health of your brain becomes easier over time.

What are the Amen Clinics?

We now have eight Amen Clinics across the United States, where we see people with complex psychiatric issues. On average our patients have 4.2 diagnoses and have failed 3.3 professionals and 5 medications. Yet after six months, if we treat them, 84% report being significantly better. We believe the reason is something we call the Amen Clinics Method, which involves detailed clinical histories (patient fill out 25 pages of information), brain SPECT imaging, neuropsychological testing, and laboratory screening that lead to more specific diagnosis and targeted treatments. In addition, we always attempt to plant brain healthy lifestyle habits in our patients lives. We have added three major innovations: neuroimaging, integrative medicine and the use of nutritional supplementation when possible. As opposed to many of our physician colleagues who report high levels of burn out, our physicians are motivated and happy, because people get better at higher than typical rates.

Personalized medicine, molecular imaging and treatment targeting are becoming an integral part of the practice of medicine. Will they play a major role in the future of neuro-psychiatry?

Yes, we believe they already are at Amen Clinics today. Psychiatry desperately needs a better way. Drugging the brain into submission is just not working. Dr. Thomas Insel, former Director of the National Institutes of Mental Health, recently wrote, *"For the antidepressants … the rate of response continues to be slow and low. In the largest effectiveness study to date, with more than 4,000 patients with major depressive disorder in primary care and community settings, only 31 percent were in remission after 14 weeks of optimal treatment … in most double-blind trials of antidepressants, the placebo response rate hovers around 30 percent … The unfortunate reality is that current medications help too few people to get better and very few people to get well."* Studies that looked at the published data from the pharmaceutical companies on antidepressant trials and the unpublished data obtained from the Freedom of Information Act found that antidepressants, except for the most severely depressed patients, worked no better than placebos or sugar pills.

To your opinion, what role do you see the Pangea-ePatient magazine play for nuclear medicine practice?

I love this magazine because it brings the latest innovations to the nuclear medicine community, which has yet to seriously embrace molecular imaging in psychiatry. There are tens of millions of people who suffer with mental health issues who could benefit from brain SPECT and PET.

Christian Scheiber
MD, PhD
Chef du service de Médecine Nucléaire –
Hospices Civils de Lyon - France

INDICATIONS DE LA SCINTIGRAPHIE DE LA VOIE DOPAMINERGIQUE PRÉ-SYNAPTIQUE PAR LE DATSCAN™ DANS LE BILAN DES SYNDROMES PARKINSONIENS

Comprendre un test comme le DaTSCAN™ demande une connaissance préalable de la voie dopaminergique qu'il explore. On appelle système dopaminergique ou voie dopaminergique l'ensemble des neurones communiquant entre eux par une molécule (neurotransmetteur) appelée dopamine. Les structures anatomiques concernées sont une région du mésencéphale (la partie compacte ('*pars compacta*') de la substance noire) et les terminaisons de ces neurones au niveau du striatum (régions de haute densité neuronale dont la structure anatomique fine révèle une organisation en couches leur donnant un aspect strié). Pour cette raison on appelle cette voie neurologique la voie nigro-striée. (Figure 1). Le striatum est composé de plusieurs amas cellulaires. Anatomiquement on distingue : le putamen localisé dans la région postérieure et le noyau caudé qui est dans la région antéro-supérieure. Ces noyaux ont des fonctions différentes complexes mais qui, pour faire très simple, sont motrices (contrôle musculaire pour le putamen) et cognitives (connexion avec les régions frontales exécutives).

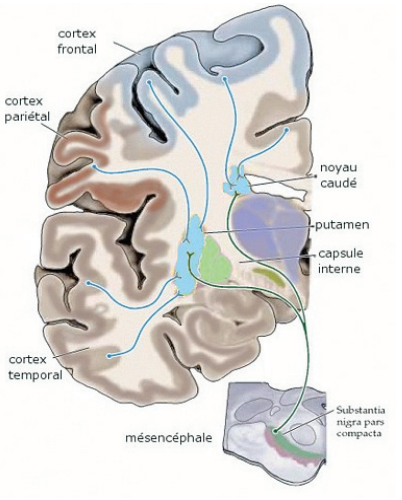


Figure 1 : schéma d'une coupe coronale du cerveau illustrant l'origine de la voie nigro-striée dans la substance noire mésencéphalique et ses terminaisons synaptiques dans le putamen et le noyau caudé (composants du striatum).

Le fonctionnement de ces régions est très complexe et n'est pas abordé ici. Cette voie est indispensable au contrôle des mouvements du corps, en particulier les mouvements automatiques (par exemple, les expressions du visage). Une atteinte fonctionnelle ou organique de cette voie se traduit par un ralentissement et/ou un contrôle insuffisant des mouvements (tremblement, lenteur, rigidité). La partie gauche du cerveau contrôle le côté droit du corps et l'atteinte de la voie dopaminergique gauche donnera un syndrome Parkinsonien droit (controlatéral) et réciproquement pour l'atteinte de la voie droite.

La maladie de Parkinson est la plus connue des pathologies de la voie dopaminergique, elle se déclare le plus souvent chez une personne de plus de 60 ans et se caractérise par des signes moteurs (le syndrome extrapyramidal), mais aussi par d'autres signes non-moteurs parfois plus difficiles à reconnaître. On sait aujourd'hui que les pathologies extrapyramidales sont très hétérogènes dans leur présentation clinique et leur pronostic. Différentes pathologies peuvent être responsables d'un syndrome Parkinsonien. Ceci ne traduit pas forcément une lésion mais, plus fréquemment, un dysfonctionnement du système dopaminergique. Parfois il s'agit d'une maladie génétique.

Le plus souvent il s'agit d'une maladie neurodégénérative par réduction trop rapide pour l'âge du nombre de neurones de la voie dopaminergique. Le cerveau a une réserve fonctionnelle qui atteint ses limites quand environ 50-60 % de la population neuronale a disparu. Dans la maladie de Parkinson il existe une dégénérescence de la substance noire (Figure 2). Il s'agit d'une synucléopathie (accumulation anormale d'agrégats de protéine synucléine). Les synucléopathies les plus fréquentes sont la maladie de Parkinson, la maladie à corps de Lewy (MCL) et les atrophies multisystématisées (AMS).

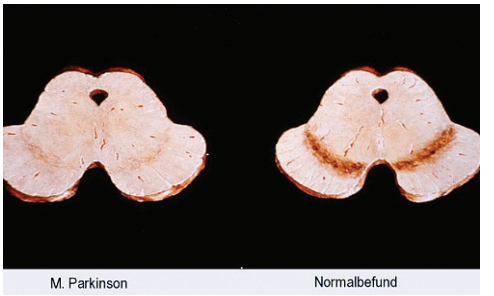


Figure 2 : coupe histologique du mésencéphale après coloration argentique des neurones dopaminergiques dans la pars compacta de la substance noire chez un patient atteint de la maladie de Parkinson (à gauche) comparée à celle d'un sujet sain. On note la décoloration traduisant la dégénérescence des neurones.

Plus rarement c'est une destruction progressive des neurones striataux (maladie de Huntington). Parfois la cause peut être un accident vasculaire qui détruit les structures ou interrompt les voies de transmissions dopaminergiques. Les syndromes Parkinsoniens atypiques regroupent un ensemble de maladies qui ont en commun une atteinte de la voie dopaminergique mais intéressent également d'autres structures anatomiques proches ou distantes. Parmi elles on retrouve la maladie à corps de Lewy, qui est également une synucléopathie proche de la maladie de Parkinson et caractérisée par une accumulation de lésions caractéristiques : les corps de Lewy, se retrouvent disséminés dans l'encéphale. D'autres synucléopathies sont plus complexes comme les atrophies multisystématisées. Mais on retrouve aussi un syndrome Parkinsonien dans la paralysie supra-nucléaire progressive (PSP) et la démence cortico-basale (DCB) qui sont des tauopathies (accumulation de protéine tau). Ces pathologies ont toutes en commun un diagnostic clinique difficile au début de leur évolution.

Ces maladies neurodégénératives n'ont pas de traitement curatif ni même protecteur (des études sont cependant en cours avec cet espoir). Cependant il existe dans plusieurs situations des traitements spécifiques, dopaminergiques et/ou agonistes dopaminergiques qui permettent une amélioration clinique au moins temporaire. C'est fréquemment le cas au début de l'évolution d'une maladie de Parkinson idiopathique qui représente 80% des syndromes Parkinsoniens. La perte neuronale se poursuit, associée à une aggravation clinique, ceci oblige une augmentation progressive du traitement avec les risques inhérents à leurs effets secondaires.

Le médecin reconnaît facilement un syndrome extrapyramidal complet mais il existe des formes frustes surtout au début de l'évolution. Un test thérapeutique permet de trancher en améliorant les signes cliniques mais seulement dans 50 % des cas.

Les neurones dopaminergiques diminuent au cours de la vie de façon significative (près de 50 % en moins sur une vie de 70 ans). Il faut en tenir compte pour l'interprétation.

L'examen DaTSCAN™ : l'exploration par neuro-imagerie de la voie dopaminergique permet de faire le diagnostic positif de son atteinte de plusieurs façons mais la scintigraphie au DaTSCAN™ est la plus commune parce que la plus disponible et la plus fiable. Le DaTSCAN™ ou ioflupane (123I-FP-CIT) est un analogue de la cocaïne. Comme cette drogue l'analogue vient se fixer spécifiquement pendant quelques heures sur une petite fraction de la population d'une protéine appelée transporteur de la dopamine localisée dans la membrane des terminaisons pré-synaptiques striatales. Ce transporteur de la dopamine (en anglais Dopamine Transporteur ou DaT, DaTSCAN™) a un rôle dans la recapture de la dopamine qui a servi dans la neurotransmission.

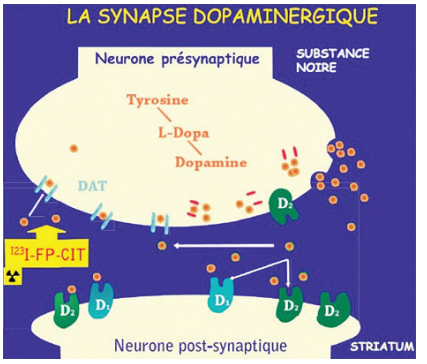


Figure 3 : schéma de la synapse dopaminergique avec entre autres un des transporteurs de la dopamine (DAT) sur le versant pré-synaptique sur lequel vient se fixer le DaTSCAN@ (123I-FP-CIT). La fixation est stable 3H après l'injection et pour environ 1H.

La molécule est marquée par un isotope radioactif, ici l'iode 123 (émetteur gamma de 159 keV). Ces molécules sont des médicaments radiopharmaceutiques. Comme tout radiopharmaceutique le DaTSCAN™ est administré à une dose « traceur » c'est-à-dire en très faible quantité : il permet de localiser et dénombrer les sites « fonctionnels » mais ne peut pas avoir d'action pharmacologique.

L'exposition est de l'ordre de 4 mSv pour 185 MBq de DaTSCAN™ injectés, c'est-à-dire de l'ordre de grandeur de l'exposition naturelle d'une année aux rayonnements ionisants. Pour respecter un principe de précaution la glande thyroïde (avide d'iode) aura été temporairement bloquée avant l'injection intraveineuse.

L'examen dure 30 minutes sur la table d'une gamma-caméra du service de Médecine Nucléaire et est réalisé trois heures après l'injection intraveineuse quand la fixation du DaTSCAN atteint un plateau. Ces caméras sont souvent couplées avec un scanner X (tomodensitomètre X) qui est utilisé pour améliorer la précision des mesures (correction de l'atténuation des rayonnements) mais aussi pour l'analyse de la morphologie cérébrale. Ces informations peuvent être utiles à l'interprétation des images devant un syndrome Parkinsonien atypique, une situation fréquente en médecine nucléaire.

Après traitement des données, la scintigraphie cérébrale représente la distribution de la radioactivité émise par le traceur. Pour tenir compte d'une fixation non-spécifique dans le cerveau (ailleurs que sur ces terminaisons neuronales dopaminergiques) on calcule des index de fixation, ou potentiel de liaison, qui expriment la concentration locale du traceur et donc du nombre de neurones fonctionnels. Ce rapport vaut pour le putamen P (activité P- activité de la région occipitale) / activité P. L'estimation de ces rapports est un challenge de mesures et des corrections doivent être appliquées (atténuation et diffusion du rayonnement, résolution spatiale de l'appareil etc..) qui sortent de l'objectif de cet article.

Contre-indications : seule la grossesse est une contre-indication, mais l'examen n'est parfois pas réalisable chez certains patients sans prémédication (par exemple chez les patients claustrophobes). Il n'y a pas de réaction allergique à l'iode avérée ce qui s'explique par la faible teneur en iode du médicament (traceur) et au

mécanisme de l'allergie à l'iode. On demande toutefois d'informer le patient et des précautions particulières peuvent être prises au besoin.

Interactions médicamenteuses et précautions à prendre avant l'examen : Le DaTSCAN™ entrera en compétition pour sa fixation sur le transporteur de la dopamine avec toute molécule (traitement, drogue) se fixant de la même façon : les dérivés de la cocaïne au premier chef mais aussi les amphétamines (par exemple la Ritaline™) et certains antidépresseurs comme la Sertraline (Zoloft™) qui doivent être arrêtés une semaine avant l'examen. Il existe d'autres médicaments qui ont des interactions plus faibles mais mesurables. La liste est connue des neurologues, gériatres, psychiatres, principaux prescripteurs de cet examen. Les éventuels traitements qui seraient conservés le jour de l'examen doivent être connus du médecin nucléaire qui en tiendra compte lors de son analyse.

IMAGERIE NORMALE - INTERPRÉTATION DES IMAGES PATHOLOGIQUES

Le DaTSCANTM se fixe préférentiellement sur le transporteur de la dopamine qui est très dense dans les terminaisons pré-synaptiques striatales des neurones dont le corps cellulaire est dans la substance noire. Sa fixation dans ces régions est proportionnelle au nombre de synapses fonctionnelles.

L'interprétation se fait par analyse visuelle des images du striatum qui sont codifiées en 4 catégories illustrées dessous, de gauche à droite : normale, anormale type 1, 2 et 3 (PCNS advisory document, 2009).

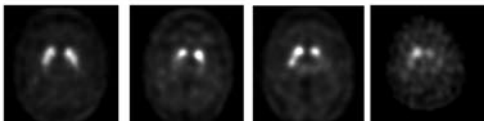


Figure 4 : images normale et pathologiques de la fixation du DaTSCANTM sur le striatum. Extrait du PCNS advisory document, 2009.

L'image normale en virgule (ou croissant) est symétrique et superposable à l'anatomie du striatum.

La physiopathologie de la maladie de Parkinson se traduit par une dégénérescence des terminaisons putaminales plus précoce que celles des terminaisons caudées et qui est rarement symétrique. L'évolution de la fixation des images reflète la dégénérescence mais n'est pas toujours superposable aux signes cliniques compte tenu de mécanismes compensateurs à différents niveaux. Le médecin nucléaire précise la voie la plus atteinte et la notion d'un gradient putamen-caudé quand il existe et témoignant d'une atteinte plus sévère du noyau putamen que du noyau caudé. En pratique les signes cliniques n'apparaissant que pour une disparition de plus de 50 % (pour certains 60 voire 70 %) des terminaisons dopaminergiques, les images sont pathologiques (type 2, 3 ou 4) lors de la réalisation de l'examen s'il existe une atteinte de la voie dopaminergique. Une atteinte au début se manifestera par une réduction de la fixation de la partie postérieure du noyau putamen gauche si les signes cliniques sont à droite (controlatéral aux signes cliniques). Une analyse fine chez la personne de plus de 70 ans demande de l'expérience car la fixation physiologique du traceur diminue avec l'âge reflétant la perte neuronale physiologique d'environ 0,6 % par an. Un gradient antéro-postérieur pathologique doit être distingué de l'image normale pour l'âge.

Depuis 2009, les caractéristiques des gamma-caméras ont été améliorées. Cela concerne, entre autres, une meilleure résolution spatiale permettant de discriminer le noyau caudé du noyau putamen, et une meilleure résolution en énergie permettant des études en double isotope (deux traceurs différents marqués par des isotopes radioactifs différents) de meilleure qualité. Ces gamma-caméras permettent d'obtenir des images diagnostiques pour des activités injectées plus faibles de l'ordre de 111 MBq (limite inférieure des recommandations internationales) réduisant ainsi l'exposition du patient en proportion et à durée d'acquisition constante (30 minutes).

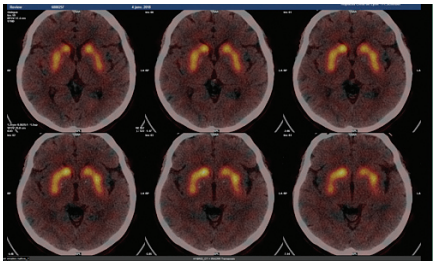


Figure 5 : coupes axiales couvrant le volume du striatum réalisées trois heures après injection de 111 MBq de ^{123}I FP-CIT (DaTSCAN™) et 30 minutes d'acquisition sur une caméra 670 CZT General Electric. Cette image normale permet de visualiser la partie antérieure (tête) du noyau caudé et le noyau putamen plus en arrière.

Il est recommandé de compléter l'analyse visuelle par une analyse semi-quantitative qui exprime les index de potentiel de liaison du patient par rapport à une base de données normale pour l'âge. Il existe plusieurs bases de données normales disponibles. Certaines sont implémentées dans des logiciels d'analyse dédiés comme le DaTQUANT® de la société General Electric (Figure 6).

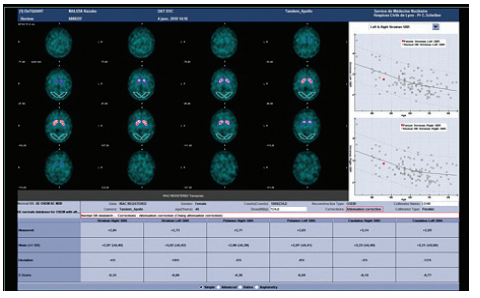


Figure 6 : le logiciel DaTQUANT® permet de comparer les résultats d'un patient avec ceux d'une base de données normales pour l'âge (ici celle du projet PPMI, USA). Sur les deux graphiques, on note un point rouge identifiant l'index du striatum du patient sur un graphe contenant les valeurs normales en fonction de l'âge (valeur moyenne et ± 95 % d'intervalle de confiance). Le tableau rapporte les valeurs des index et l'écart à la moyenne pour l'âge du patient.

La dispersion des valeurs normales autour de la moyenne pour un âge donné reflète en partie des

incertitudes instrumentales mais principalement une variabilité physiologique. Le DaTSCANTM permet d'estimer une diminution régionale (une partie du striatum) de l'ordre de 20 %, bien inférieure à celle qui va donner des signes cliniques. L'indication de l'examen se fait sur la présence de ces signes (le syndrome extrapyramidal) et en conséquence les index sont toujours très pathologiques le jour de l'examen si la maladie est présente. De fait, il est rare de constater une atteinte dopaminergique toute débutante, limitée à la partie postérieure d'un des putamen. L'analyse visuelle reste nécessaire. Il sera parfois difficile d'éliminer une atteinte débutante discrète chez la personne âgée si elle est symétrique.

Les images « normales » pour l'âge se retrouvent jusqu'à un âge avancé (Figure 7). Physiologiquement on note une diminution modérée de la fixation de la partie postérieure du putamen qui est en général symétrique.

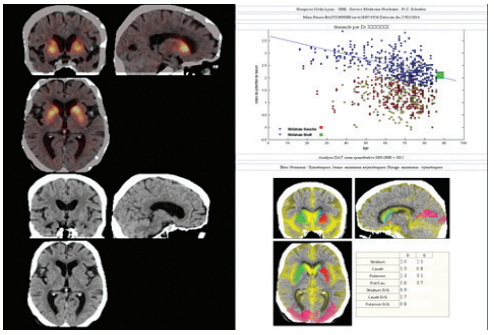


Figure 7 : exemple d'un DaTSCAN™ normal chez un patient de 90 ans dont les index ont été calculés avec un autre logiciel. Le graphe donne en bleu les valeurs normales en fonction de l'âge et en rouge les valeurs pathologiques usuellement rencontrées dans un groupe apparié en âge.

Certaines pathologies se traduisent par une perte plus homogène de la densité de terminaisons synaptiques et l'analyse visuelle n'est plus performante. Les effets éventuels d'une interaction médicamenteuse (compétitive) sont mesurés par l'analyse semi-quantitative comme chez cette patiente qui n'avait pas suivi la demande d'arrêt des amphétamines (Figure 8). Il n'est pas possible de différencier les deux examens par l'analyse visuelle. Ce sera le cas pour toute diminution globale/homogène de la fixation comme on peut parfois la rencontrer dans des indications pour syndrome Parkinsonien atypique.

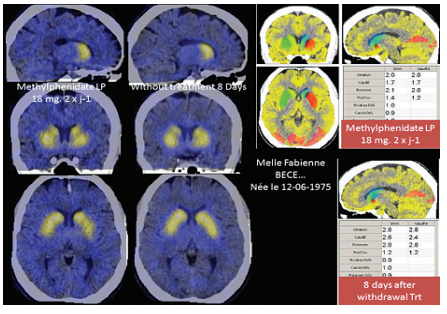


Figure 8 : deux examens DaTSCANTM d'une jeune patiente sous traitement par amphétamines et qui n'avait pas arrêté son traitement. La fixation est homogène mais diminuée. A droite l'image et les index sont redevenus normaux 8 jours après sevrage.

LES INDICATIONS DU DATSCAN™ EN ROUTINE CLINIQUE

Le diagnostic de **maladie de Parkinson** est clinique devant la mise en évidence du syndrome extrapyramidal mais, au début de la maladie, la symptomatologie peut être fruste et/ou atypique. Ce patient de 45 ans présentait un tremblement du membre inférieur droit depuis quelques mois et le DaTSCANTM a été demandé en raison de son jeune âge. Il montre une atteinte surtout du putamen gauche dont on ne distingue plus que le 1/3 antérieur et de la partie postérieure du putamen droit qui était asymptomatique : ces images sont assez caractéristiques de maladie de Parkinson débutante (Figure 9). Les images sont pratiquement toujours anormales des deux côtés mais asymétriques, en controlatéral des signes cliniques. L'atteinte putaminale (la réduction de la fixation) est toujours plus marquée avec un gradient antéro-postérieur. Ces images reflètent l'évolution naturelle de la dégénérescence de la substance noire. L'index striatal du côté le moins atteint peut rester dans la moyenne pour l'âge au début de l'évolution chez un patient sans symptomatologie extrapyramidale franche.

En imagerie nous utilisons des échelles de couleur pour faire apparaitre des différences significatives dans les images. Pour le DaTSCAN™ elle discrimine les régions de moins de 50 % de la normale (seuil symptomatologie clinique). Les images DaTSCAN™ ne reflètent que la fixation du traceur sur le transporteur de la dopamine et les mécanismes compensateurs peuvent expliquer une partie des discordances entre les signes scintigraphiques et la clinique souvent en retrait par rapport aux valeurs mesurées. En particulier au début de la maladie.

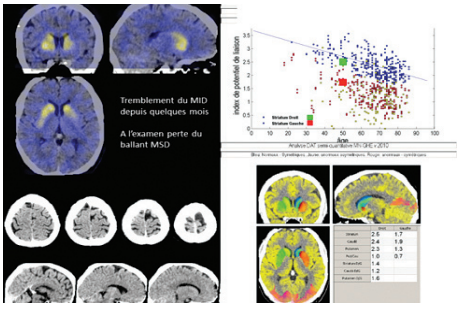


Figure 9 : image caractéristique d'un patient, quelques mois après l'apparition des signes cliniques (ici tremblement du membre inférieur droit). – On note l'atteinte putaminale gauche et déjà de la partie postérieure du putamen droit. L'index gauche (carré rouge) est en-dessous de la valeur normale pour l'âge. L'index striatal droit reste dans les limites de la normale bien que la partie postérieure du putamen soit atteinte. Nécessité d'une interprétation visuelle et numérique.

La première indication du DaTSCAN™ a été le diagnostic différentiel d'un tremblement essentiel atypique. Le tremblement essentiel n'a pas d'étiologie connue, il est fréquent dans la population. Quand il est typique, ce qui est le plus souvent le cas, c'est un tremblement fin d'attitude. Dans certaines situations il peut être/devenir atypique faisant suspecter une atteinte de la voie dopaminergique. L'examen au DaTSCAN™ est strictement normal pour l'âge comme l'illustre le résultat de l'examen ci-dessous devant un

tremblement essentiel dont le diagnostic remonte à plus de 10 ans, mais qui se complète depuis quelques mois d'une composante de repos et l'apparition d'autres signes de la série extrapyramidale (hypomimie) (Figure 10).

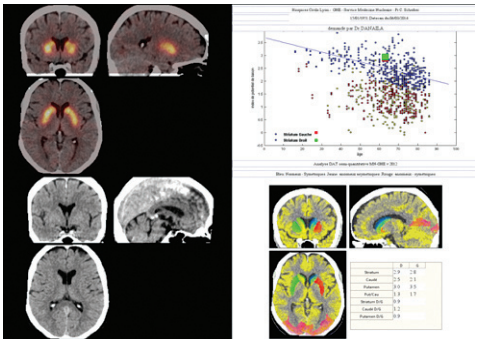


Figure 10 : image DaTSCAN™ normale chez un patient présentant une évolution récente de son tremblement qualifié d'essentiel, connu depuis 10 ans.

Plus rarement il s'agira d'un **diagnostic différentiel entre une dégénérescence dopaminergique vraie et un Parkinson iatrogène** : le diagnostic d'un syndrome extrapyramidal (syndrome Parkinsonien) chez un patient sous neuroleptiques (y compris dernière génération). Les neuroleptiques agissent sur la voie dopaminergique en bloquant les récepteurs post-synaptiques. Le syndrome extrapyramidal clinique est donc identique à celui observé par dégénérescence pré-synaptique. Le syndrome post-neuroleptique peut persister malgré l'arrêt du traitement et peut aussi survenir rapidement ou après des dizaines d'années de prise médicamenteuse chez des patients psychotiques. Le patient peut en parallèle présenter un début de dégénérescence dopaminergique qui se révèle cliniquement du fait d'un blocage post-synaptique additionnel thérapeutique.

Le DaTSCAN™ sera normal ou pathologique en fonction de la contribution éventuelle d'une dégénérescence et permettra de l'estimer si une analyse semi-quantitative est effectuée. Les demandes cliniques sont très variées et souvent complexes comme chez ce patient âgé de 85 ans qui présentait un syndrome extrapyramidal avec des troubles cognitifs, l'ensemble aggravé par les neuroleptiques avec des antécédents d'accident vasculaire ischémique frontal droit. Le DaTSCAN™ était strictement normal pour l'âge permettant d'exclure une atteinte de la voie dopaminergique pré-synaptique (Figure 11).

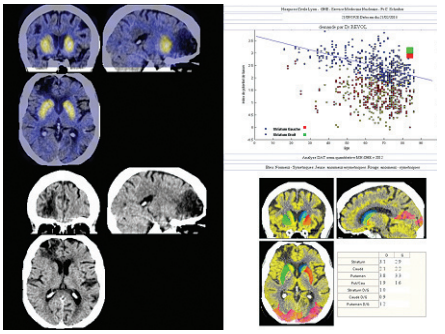


Figure 11 : en haut à gauche image DaTSCAN™ normale chez un patient présentant un syndrome frontal post-ischémique avec syndrome extrapyramidal récemment aggravé par la prise de neuroleptiques. A droite la courbe confirme des index normaux pour l'âge.

Plus rarement se posera le diagnostic d'un pseudo-syndrome-parkinsonien chez une patiente psychiatrique avec un syndrome extrapyramidal dont un tremblement d'origine psychogène. L'image DaTSCAN™ de contrôle et ses valeurs semi-quantitatives se sont avérées strictement normales. Il est utile de souligner l'importance d'un recalage précis des images (méthode automatique ou manuelle) car un écart peut conduire à une erreur d'interprétation devant une asymétrie qui serait positionnelle. C'est ce qui était arrivé chez cette patiente où un premier examen, de qualité insuffisante, avait conclu à une atteinte dopaminergique débutante (Figure 12).

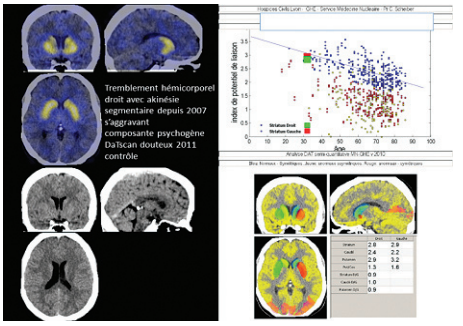


Figure 12 : DaTSCAN™ strictement normal chez cette jeune femme sans antécédent psychiatrique mimant parfaitement un syndrome Parkinsonien.

SYNDROME PARKINSONIEN ATYPIQUE

L'atteinte neurologique concerne d'autres systèmes en plus du système dopaminergique. La scintigraphie DaTSCAN™ est en général anormale mais le type d'anomalie n'est pas caractéristique d'une pathologie particulière. Ces maladies sont les suivantes : atrophie multisystématisée (AMS), Paralysie supranucléaire progressive (PSP), dégénérescence cortico-basale (DCB) et la maladie à corps de Lewy diffus (MCL). A un stade évolué, les troubles cognitifs sont tels que le patient devient dépendant et on parle de démence.

Ces pathologies neurologiques sont complexes et leur phénotype clinique très divers. Souvent seule l'évolution clinique, parfois après plusieurs années, permettra le diagnostic. Les signes radiologiques (IRM), d'atrophie le plus souvent, sont souvent discrets à la première consultation. Un des avantages de la médecine nucléaire est de montrer des signes de dysfonctionnement précoce, ici de la voie dopaminergique, dans un contexte d'imagerie cérébrale (encore) normale.

L'atteinte dopaminergique pré-synaptique explorée par le DaTSCAN™ ne donne qu'exceptionnellement une information pertinente sur la pathologie en cause, mais la preuve de cette atteinte et son étendue est une aide précieuse pour le clinicien. Si la séméiologie de l'image DaTSCAN™ est rarement caractéristique, le médecin pourra s'appuyer également sur les signes morphologiques obtenus par le scanner X et sur les résultats de l'analyse semi-quantitative.

Maladie à corps de Lewy disséminés (MCL) : cette maladie neurodégénérative est en fréquence la seconde cause de démence derrière la maladie d'Alzheimer avec environ 5-15 % de l'ensemble.

La MCL est due à des lésions spécifiques, les corps de Lewy, avec des dépôts anormaux d'une protéine synucléine (comme la maladie de Parkinson). Les corps de Lewy se retrouvent dans tout le cerveau et pas seulement dans la substance noire (maladie de Parkinson). Elle peut se développer seule ou associée à une maladie d'Alzheimer (MA) ou une maladie de Parkinson. Le DaTSCAN™ est fortement abaissé chez près de 85% des patients (Figure 13) alors qu'il reste normal pour l'âge chez un patient atteint de maladie d'Alzheimer.

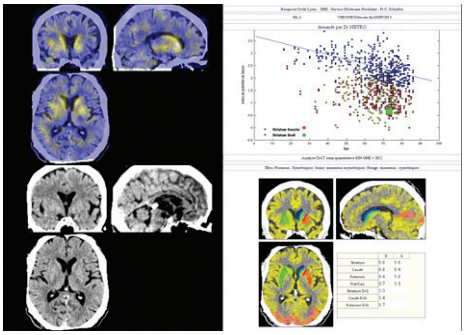


Figure 13 : DaTSCAN™ d'un patient atteint d'une maladie à corps de Lewy qui montre une fixation très faible du striatum (images, index) alors que le syndrome extrapyramidal était très discret. Dans cette maladie le DaTSCAN™ est en général symétrique et montre une très faible fixation.

Le diagnostic est parfois difficile en raison de la discrétion des signes extrapyramidaux et l'importance des troubles cognitifs. Le diagnostic est important à effectuer car la MCL évolue plus rapidement que la MA et surtout ces patients sont très sensibles aux neuroleptiques qui sont cependant formellement contre-indiqués. L'examen par le DaTSCAN™ est un des critères qui permet de définir la probabilité diagnostique de cette pathologie chez des patients présentant des troubles cognitifs et peu ou pas de symptômes extrapyramidaux.

Le DaTSCAN™ est indiqué quand la recherche d'argument en faveur d'une maladie à corps de Lewy est nécessaire, entre autres, pour le diagnostic différentiel avec la maladie d'Alzheimer. La gamma-caméra permet de réaliser des examens en double isotopes permettant d'explorer simultanément la perfusion cérébrale, par exemple par l'HMPAO ^{99m}Tc (gamma, 140 keV), et la voie dopaminergique par le DaTSCAN™ (Figure 14). Les hypoperfusions éventuelles sont corrélées avec les signes d'atrophie (scanner X) et interprétées conjointement avec le résultat du DaTSCAN™.

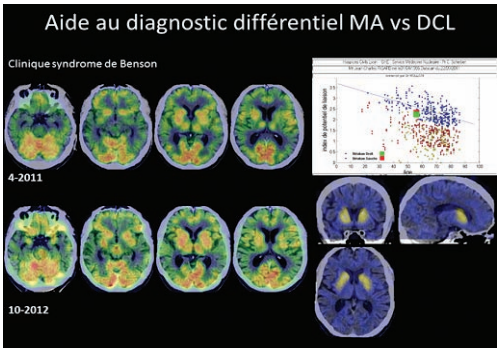


Figure 14 : un examen hybride de perfusion cérébrale à l'HMPAO et DaTSCAN™ chez un patient présentant des signes en faveur d'une maladie d'Alzheimer atypique (syndrome de Benson) mais dont le diagnostic différentiel avec une maladie à corps de Lewy était difficile. L'examen DaTSCAN™ était strictement normal permettant de réduire le risque de MCL et la scintigraphie cérébrale (réalisée en 2011 et 2012) montre la stabilité des hypoperfusions étendues telle qu'on les rencontre dans la maladie d'Alzheimer (par exemple).

L'Atrophie multisystématisée se rencontre sous la forme Parkinsonienne dominante (AMS-P, chez 80% des patients) d'expression clinique proche du Parkinson, mais d'évolution rapide (6-8 ans) avec d'importants signes d'atteinte autonome et une forme cérébelleuse (AMS-C, 20 % des patients). Dans l'AMS-C, en sus de l'atteinte dopaminergique (DaTSCAN™ pathologique), il existe, entre autres, une atteinte du cervelet avec des troubles de la coordination des mouvements (ataxie), des troubles du système nerveux autonome et des signes d'atteinte de la voie pyramidale (motricité volontaire). L'imagerie morphologique couplée (examen hybride avec un scanner X couplé) permet de donner une orientation diagnostique sur la reconnaissance d'une atrophie cérébelleuse (AMS-C) comme chez ce patient de 72 ans (Figure 15).

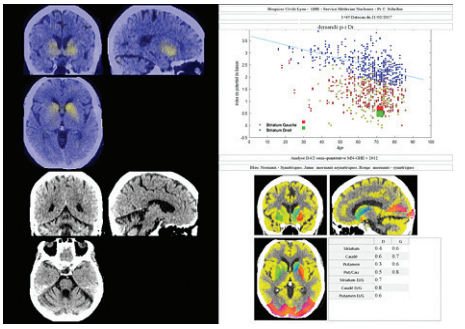


Figure 15 : DaTSCAN™ en faveur d'une atteinte dopaminergique pré-synaptique bilatérale sévère dans un contexte clinique évoquant une AMS-C. Le diagnostic est rendu plus probable encore sur l'image TDM d'atrophie cérébelleuse.

La Paralysie supranucléaire progressive (PSP) est une tauopathie comme la maladie d'Alzheimer qui se caractérise par des chutes précoces et une limitation progressive des mouvements des yeux (l'oculomotricité). Chez ces patients présentant un syndrome Parkinsonien atypique, l'atteinte dopaminergique est souvent globale et symétrique ce qui rend moins probable une maladie de Parkinson idiopathique classiquement asymétrique et intéressant plus le putamen (au stade du diagnostic).

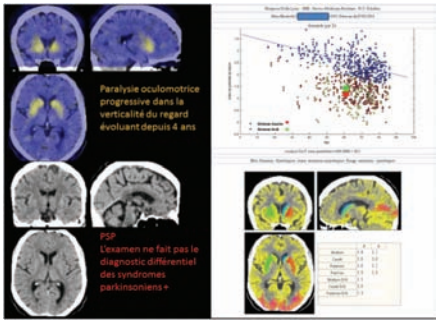


Figure 16 : DaTSCAN™ d'une patiente atteinte d'une paralysie de l'oculomotricité progressive faisant craindre une PSP. L'atteinte est bilatérale et asymétrique. Sur l'image DaTSCAN™ seul l'abaissement global de la fixation du striatum droit (index droit abaissé) permet d'évoquer une pathologie autre qu'une maladie de Parkinson. L'imagerie morphologique est encore subnormale à ce stade.

La Dégénérescence cortico-basale (DCB) associe une atteinte corticale (en général fronto-pariétale) et une atteinte striatale homolatérale. Les signes cliniques sont

classiquement moteurs sous forme d'un trouble d'aggravation progressive de la réalisation de certains mouvements (apraxie motrice) mais la présentation clinique est souvent dominée par les troubles cognitifs (atteinte frontale). DCB et PSP sont présentées comme des entités distinctes pour faciliter le diagnostic et la compréhension de ces pathologies complexes qui sont parfois regroupées sous la dénomination de complexe de maladie de Pick. L'examen au DaTSCAN™ est classiquement très asymétrique permettant de mesurer l'atteinte dopaminergique striatale et c'est l'imagerie morphologique couplée qui apporte une information complémentaire nécessaire en objectivant une atrophie corticale du même côté du cerveau. Celle-ci est souvent discrète et demande, comme pour le DaTSCAN™, un recalage, voire une mise en correspondance dans un espace anatomique standard, pour être étudiée. Quand les signes sont discrets, il est utile de pratiquer un examen en double isotope associant au DaTSCAN™ un traceur de la perfusion comme l'HMPAO-^{99m}Tc qui confirmera la réduction de la perfusion de la région anatomique suspecte d'atrophie. L'exemple ci-dessous est académique, les signes d'atrophie sont suffisamment marqués pour permettre d'évoquer le diagnostic sans l'aide d'une scintigraphie de perfusion (Figure 17).

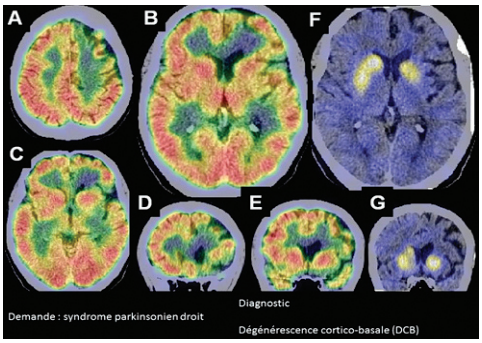


Figure 17 : A à E scintigraphie de perfusion cérébrale à l'HMPAO montrant la diminution de la perfusion corticale frontale gauche bien corrélée avec les signes d'atrophie. F et G DaTSCAN™ de ce patient qui présentait un syndrome Parkinsonien droit montrant la diminution de la fixation du putamen. Dégénérescence cortico-basale.

Les syndromes Parkinsoniens peuvent également être secondaires à une atteinte vasculaire et le DaTSCAN™ permettra d'objectiver l'étendue de l'atteinte dopaminergique pré-synaptique. Pour un compte-rendu plus complet, on s'appuiera sur l'imagerie morphologique couplée qui localise et précise l'étendue des séquelles ischémiques comme chez ce patient qui présente un syndrome Parkinsonien gauche séquellaire d'un accident vasculaire ischémique de la branche profonde de l'artère Sylvienne gauche et responsable d'une destruction partielle du striatum (Figure 18).

EN CONCLUSION

Le DaTSCAN™ est un examen de routine clinique performant, bien codifié et fiable pour une estimation de l'atteinte du système dopaminergique pré-synaptique sous réserve d'un sevrage de traitements compétitifs pour le transporteur de la dopamine.

Dans la majorité des situations cliniques, le clinicien peut résoudre le problème diagnostic par un examen neurologique et parfois aidé par une IRM cérébrale. La situation est plus difficile au début de l'expression clinique de la maladie y compris pour la maladie de Parkinson. Devant un syndrome Parkinsonien atypique, le DaTSCAN™ peut apporter une contribution au diagnostic précoce. Si le retard au diagnostic n'a pas d'incidence sur l'évolution naturelle de ces maladies, il est mal vécu par les patients et leur famille et entraîne des coûts supplémentaires. Le diagnostic précoce permet parfois de soulager un patient qui répondrait à la thérapeutique spécifique.

Le DaTSCAN™ est indiqué dans le diagnostic différentiel d'un tremblement essentiel, le diagnostic différentiel entre une maladie d'Alzheimer et la maladie à corps de Lewy. Le DaTSCAN™ permet d'estimer une composante dégénérative éventuelle devant un syndrome extrapyramidal chez un patient sous neuroleptiques.

Si une analyse visuelle suffit le plus souvent pour répondre au clinicien sur la présence ou l'absence d'une atteinte et sa sévérité, elle n'est pas spécifique de la pathologie sous-jacente. L'examen est d'autant plus informatif qu'une analyse semi-quantitative est réalisée, par comparaison avec une base de données normale en fonction de l'âge. Dans tous les cas, un prérequis à l'analyse suppose un réalignement optimal des images.

Dans ces pathologies complexes, parfois multifactorielles, une orientation diagnostique peut être proposée si l'on dispose d'une imagerie hybride associant un scanner X qui permet d'inclure les informations morphologiques dans l'interprétation (atrophie, séquelles ischémiques...). Une aide supplémentaire est apportée par la double scintigraphie associant l'imagerie de perfusion et le DaTSCAN™ qui est réalisée simultanément. ■

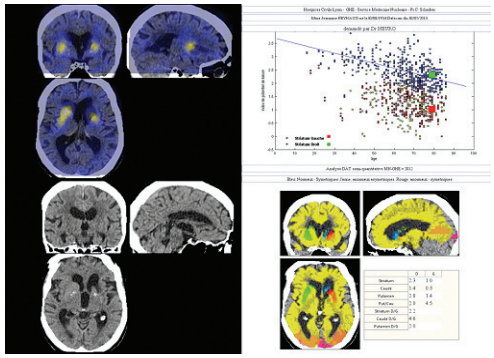


Figure 18 : examen DaTSCAN™ d'un patient présentant un syndrome Parkinsonien secondaire à un accident vasculaire ischémique Sylvien gauche profond ayant détruit une partie du striatum. Le clinicien souhaitait éliminer la coexistence d'une maladie dégénérative. La valeur strictement normale du striatum droit est en faveur d'une intégrité de la voie dopaminergique droite. Le syndrome Parkinsonien est secondaire à l'accident vasculaire.

Andrew Ross
President CANM

THE CANM IS CHAIRING THE INTERNATIONAL TASK FORCE ON THE HARMONIZATION OF RADIO-PHARMACEUTICALS' REGULATIONS

Radiopharmaceutical regulations around the world are disparate and in some ways desperate. The non-uniformity and in some cases retrogressive nature continues to adversely affect patient access to these vital medical substances. Additionally, costs are significantly higher which in its own way further jeopardizes access. In many jurisdictions, this is one of the major jeopardies to the practice of nuclear medicine.

The biggest issue is regulators the world over largely view these in the same space as drugs from major pharmaceutical companies. Those familiar with the specialty of nuclear medicine understand that this overly simplistic analogy is flawed. Over the past decade there have been some efforts at reform of these to try and recognize the more unique nature of radiopharmaceuticals, however there is still a long way to go. The positives are currently there are efforts at international harmonization of pharmaceutical regulations. This does offer an opportunity for positive change; however, the area of nuclear medicine and its products are minuscule relative to the huge economy of cold pharma.

In Canada, the Canadian Association of Nuclear Medicine has developed with the Canadian Association of Radiopharmaceutical Scientists a constituted working group with the regulator to try and positively influence progress in this domain. From this, it has become obvious that a more broad reaching effort to stimulate wider efforts at regulatory reform and harmonization would be beneficial to here but as well in other many jurisdictions. Based on this, the Canadian Association of Nuclear Medicine has approached sister organizations around the globe to discuss these issues and attempt to develop concrete plans to help influence reform.

Additionally and in more broad reaching effort, the International Atomic Energy Agency Association has convened working groups composed of both regulators from the developing and developed world as well as representatives of the Nuclear Medicine community. This effort is viewed as a fantastic opportunity to further these efforts at international harmonization. The IAEA has a strong positive and impartial reputation while at the same time being intimately understanding of the practice. Such thoughts can be beneficial to both developed countries with strong regulatory practices to help them understand the uniqueness of the substances aiding international harmonization while concurrently providing a solid platform for developing countries to build safe regulatory practices.

Meetings have occurred involving the international Nuclear Medicine societies and community. These will continue to occur and are inclusive to all. Currently this involves the EANM, SNMMI, ANZSNM and the CANM. Expansion to include Asia and South America is underway. Additionally, the IAEA is in the process of developing a position paper based on discussions which will help form a platform moving forward.

Overall it is hoped that these efforts will help harmonize practices and reduce regulatory burden on what substances that have exceptional safety profiles and to date have been significantly adversely affected in terms of patient availability. ■

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Association canadienne de médecine nucléaire

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- ✓ Its ability to **promote, develop and support** the use of medical isotopes **in the emerging countries**.
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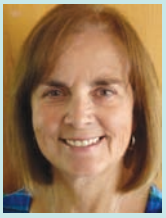

Hélène Samson

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The Canadian Association of Nuclear Medicine
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CANM Annual Scientific Meeting 2019

February 7-10, 2019

Hôtel Le Concorde
Québec City

Picture taken at the Society of Nuclear Medicine and Molecular Imaging meeting in Denver, 2017

From left to right:
DR. Francois Lamoureux, president elect CANM
DR. Bennett Grennspan, president SNMMI
Dr. Andrew Ross, president CANM
Dr. Satoshi Minoshima, president elect SNMMI

SISTER ORGANIZATIONS

SNMMI Society of Nuclear Medicine and Molecular Imaging
EANM European Association of Nuclear Medicine — Biomedical Imaging and Therapy for Personalized Healthcare
World Federation of Nuclear Medicine and Biology
AIPES
ARCENM
ASNC
AFNMB Asia Oceania Federation of Nuclear Medicine and Biology
IAEA International Atomic Energy Agency
alasbimn Asociación Latinoamericana de Sociedades de Biología y Medicina Nuclear

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Dr. Andrew Scott, M.D.,
President of the World Federation of Nuclear Medicine and Biology.

Sze Ting Lee, M.D.,
Secretary-General, WFNMB

WORLD FEDERATION OF NUCLEAR MEDICINE AND BIOLOGY (WFNMB) CONGRESS 2018

The World Federation of Nuclear Medicine and Biology (WFNMB) is the global umbrella for nuclear medicine regional societies throughout the world, linking the practice and promotion of nuclear medicine throughout the Americas, Asia, Africa, Europe and Oceania. It was founded in 1970 and one of its unique features is the integration of developed and developing countries – to create opportunities for shared activities such as research and education in the world.

The WFNMB quadrennial Congresses is considered as the "Olympics of Nuclear Medicine Conferences", and has become a major international forum for the presentation of all aspects nuclear medicine basic, applied and clinical nuclear medicine research, diagnosis and treatment of various disorders. The evolution of nuclear medicine practice has resulted in the integration of hybrid imaging into the program of this caliber of meetings, and a multidisciplinary approach in this era of personalized medicine.

The 12th Congress of the WFNMB will be held from the 20th to 24th of April, 2018 in Melbourne, Australia. The theme of this congress is to promote "Global Translation of Molecular Medicine", incorporating the

translation of basic laboratory research to clinical practice, establishment of clinical and technical standards, and the translation of molecular medical technology to developing countries for the benefit of patients worldwide.

This Olympics will be opened by a plenary to be given by Prof Brian Schmidt – The 2011 Nobel Laureate in Physics, Vice Chancellor and President of Australian National University.

The cutting edge, multidisciplinary scientific program will include an outstanding program of four high level plenary sessions, including a second Nobel Laureate speaker – Prof Peter Doherty – The 1996 Nobel Laureate in Medicine.

They will be supported by over 100 internationally renowned speakers speaking in >70 continuing education sessions, and large poster presentation sessions which will be both enjoyable and educational to attendees.

There will be 13 different tracks, including oncology, neurology, cardiology, endocrinology, pædiatrics, musculoskeletal, molecular imaging, nuclear medicine innovations, theranostics, physics, instrumentation, and radiopharmaceutical sciences. The program will contain sessions which will appeal to nuclear medicine specialists, radiologists, medical imaging trainees, physicists, scientists, technologists, nurses, and the broader medical and scientific community.

Please visit the website: www.wfnmb2018.org for more information.

André Gagnon
Président – Isologic Radiopharmaceutiques Novateurs
Montreal, Canada

ANDRE GAGNON
CEO Isologic

You have been actively involved in nuclear medicine for many decades. Looking back at your career, what are the most significant changes that you have witnessed in the field?

The advances in nuclear medicine have been astounding. In recent decades, it has become a key resource in the management of patients with cancer, neurological and cardiac diseases. As the industry has grown, we have seen massive changes in technology, regulation and funding. As we move forward, there are exciting opportunities to improve patient outcomes using nuclear medicine.

Since I became involved in nuclear medicine, the practice has evolved from the early days of planar imaging with a few single photon imaging radiopharmaceuticals; to positron emitting agents with hybrid scanners that are now considered essential for standard of care. Advances to hybrid imaging, the availability of new radiopharmaceuticals for diagnosis and therapy, and the development of molecular imaging have dramatically changed the field. The industry has been remarkably successful in finding novel processes to provide safer and more efficient solutions in the name of patient care.

The regulatory environment has also brought massive changes to the industry, following the unfortunate sterility failures at compounding facilities in the United States. The inability of some firms to maintain the highest quality has at times had tragic consequences, leading to patient injury and death. Quality and safety standards rose dramatically following the release of more stringent US FDA regulations (e.g. USP <797>), and greater focus on cGMP compliance by Health Canada. Hospitals have been mandated to enhance the management of their compounding practices, or source unit dose radiopharmaceutical services from Health Canada-compliant radiopharmacies. Quality is paramount in this industry, and old practice standards can no longer meet patients' expectations of safety and accuracy. Companies like ISOLOGIC have quickly evolved to ensure customers can be confident in the care we provide.

With technological advancements and the evolution of the industry, the funding environment has become more challenging. Provincial efforts to control rapidly increasing healthcare costs have resulted in a decreased appetite to pay for medical imaging. At the same time, pressure has been placed on nuclear medicine physicians to become gatekeepers of public healthcare funds, while simultaneously requiring them to provide patients with the best medical interventions to help with their conditions. This creates a challenging balancing act, where physicians must weigh public costs versus patient outcomes. The nuclear medicine industry needs to make a concerted effort to drive cost-efficient solutions, and a consistent strategy to advocate for the effective patient outcomes generated by nuclear imaging, to strengthen its use as a standard procedure.

A few years ago, you became the CEO of ISOLOGIC. What are the vision and mission of ISOLOGIC, and what does the future hold?

My time at ISOLOGIC has been one of the most exciting periods of my career. Our mission is simple: we want to provide physicians with the most clinically relevant PET and SPECT radiopharmaceuticals in a safe, reliable manner, and ultimately help save patients' lives.

Our goal is to become a global leader and a central point of entry for breakthrough radiopharmaceuticals in Canada. We want to be the most trusted quality care partner in the industry, and to help ensure that patients in this country receive world-class care.

ISOLOGIC operates five SPECT radiopharmacies and two cyclotron facilities across Canada, and we're the only radiopharmacy company in the country that owns and operates its own logistics and delivery unit. We deliver over 650,000 doses annually, with the aim of being the provider

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One of the biggest challenges in this business is the fragile Mo99 supply chain. Unexpected reactor maintenance or downtime can be very disruptive to the supply of isotopes. We strategically sources from all generator suppliers to provide a continuous supply to our customers. With our diverse sourcing, we are committed to ensuring the Canadian healthcare community continues to have access to a consistently reliable and efficient supply of radiopharmaceuticals.

After many decades of very few new nuclear medicine tracers, it seems that there is now a plethora of specific molecular radioactive imaging probes. In your view, which are the most clinically promising?

The speed with which imaging has advanced has been incredible. Molecular imaging is embracing these changes and using different strategies to understand disease states and physiology.

Numerous probes such as ^{18}F-ethyltyrosine, ^{18}F-fluoromisonidazole, and ^{18}F-labeled choline have proven their clinical utility and help to address very niche clinical indications. These probes are certainly relevant but will be challenging to bring to market in Canada, because of the small number of people who might require these scans.

Neuroendocrine tumor (NET) imaging with DOTA tracers labeled with Ga^{68}; prostate-specific membrane antigen (PSMA) labelled with either F^{18} or Ga^{68}; and Beta Amyloid agents labelled with F^{18} such as Neuraceq®, are addressing larger markets and might be a more relevant investment for industry, because they offer greater promise of financial viability.

The fact that DOTA and PSMA tracers are also being used for imaging and potentially treating patients with a different isotope (such as Lu-177), makes these theranostic agents particularly interesting. Their potential applications make them a very exciting area to explore, as they may be of great value in supporting and strengthening the future of personalized medicine

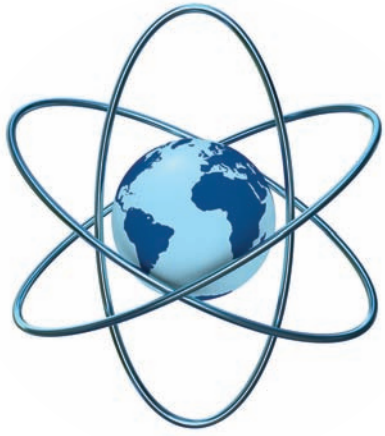
The approval of new radiopharmaceuticals has become a notoriously difficult process in Canada and many parts of the world. With the explosion of health care costs over the past two decades, governments have limited access to costly new technologies. How do radiopharmaceutical companies approach the hurdles of regulatory approval and financial reimbursements?

The last decade has brought profound changes in the way the nuclear medicine industry interacts with the government. On one hand, Health Canada has been proactive in trying to modernize the country's healthcare system. They have been responsive to industry concerns about the authorization of Schedule C drugs in general, and PERs in particular. Understanding the difficulties that come with the size of the Canadian market, Health Canada has been supportive and, in some instances, has worked to streamline the regulatory hurdles to accommodate the limitations of our industry.

On the other hand, the healthcare industry has been grappling with chronic underfunding from provincial health ministries. The failure to recognize the precarious situation of the radiopharmaceutical industry is the largest obstacle we face, and how we meet this challenge is critical.

Our current goal is to collaborate with all stakeholders in the government, in hospitals, and in our industry to help them better understand the important role of radiopharmaceuticals and rethink the clinical and economical effectiveness of our modality, to further encourage the proper use of our technology. We look forward to working with our peers and our customers to continue moving the nuclear medicine industry towards sustainability, reliability, and affordability.

As a market leader, we are optimistic that we can overcome these challenges. We will continue to use innovative approaches to provide new clinical options to healthcare professionals, and to assist in the diagnosis and treatment of life threatening diseases.



WORLD FEDERATION OF NUCLEAR MEDICINE & BIOLOGY

PRESIDENCY CANDIDATE : Dr. Jean-Luc Urbain

Jean-Luc Urbain
M.D., Ph.D., CPE
Past President, CANM

- MD: University of Louvain, Belgium
  - Board Certified in Internal Medicine
  - Board Certified in Nuclear Medicine
- Ph.D.: Temple University, Philadelphia
  - Molecular Biology and Genetics
- CPE: Certified Physician Executive
- University of Louvain, Temple University, Cleveland Clinic, University of Western Ontario, VHA, Wake Forest University
- Membership: EANM, SNMMI, CANM
- > 1000 lectures in Europe, NA, Asia, SA, Middle East, AF
- Radiant Educational Award, Canada; Homi Babbha Scientific Award, India
- Main interests: Personalized Medicine, Theranostics, NM Education

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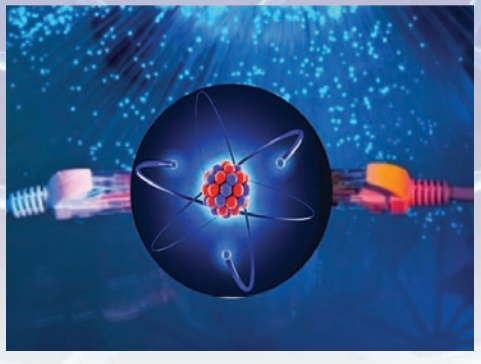


Theodore Henderson, MD, PhD
Brain Health Centers, Inc
Denver, Colorado, USA

BRAIN SPECT IMAGING IN NEUROPSYCHIATRIC DIAGNOSIS AND MONITORING

Mention SPECT (single photon emission computed tomography) brain imaging to a group of psychiatrists and you are likely to hear groans or angry retorts. The resistance to actually looking at brain function in psychiatric patients is startling. The well water seems to have been poisoned in psychiatry, perhaps by over-zealous marketing in the past. Early claims which were unsupported by clinical research data created a sense of distrust among psychiatrists. Oddly, nuclear medicine physicians have followed suit. Brain SPECT scanning has been underutilized and, frankly, underappreciated for decades. Nevertheless, during that same timespan, remarkable progress has been made in the hardware, software and clinical research revolving around brain SPECT scans. Herein, some of the more interesting advances will be explored and integrated into the practice of today's busy nuclear medicine department.

TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is a complex disorder, as it varies depending on the part of the brain involved, the extent of injury, the post-injury protocols/progress, and immune/inflammation interactions.[1] While there are over 2.5 million emergency room visits for suspected TBI in the United States annually,[2] it is suspected that an additional 4 million mild TBI's occur each year. Studies of civilians with TBI reveal that 49% develop a new psychiatric illness in the year subsequent to injury.[3,4] Victims of head injury in motor vehicle accidents also have a higher rate of post-traumatic stress disorder (PTSD) compared to those with orthopedic injuries 44% vs 11%).[5] This overlap of TBI and PTSD can be particularly daunting among military troops and veterans. In the United States, roughly 20 veterans committed suicide each day in 2014, 2015, and 2016.[6] PTSD and TBI have a significant contribution to the sense of despair and futility that lead veterans to take their own lives.[7] A sense of hopelessness for those veterans with TBI may stem from the common medical assertion that there is no treatment for TBI. In addition, veterans with PTSD or depression are often reluctant to seek help because they feel PTSD and depression are not real brain disorders, but a failure of character. Shame, guilt, fear of medications, and a lack of confidence in the therapies offered are also factors that keep veterans isolated, alone, and untreated.[8-10] Current estimates indicate that 13.5% of returning military report persistent PTSD symptoms.[11] According to the Congressional Budget Office, an estimated 400,000 service men and women have TBI or PTSD.[12] Alas, among the 400,000 or more Veterans with either TBI or PTSD, there is tremendous overlap both in terms of diagnosis and of symptomatology. The overlap is estimated to be 33% to 42%,[13] but may be considerably higher. A study of patients in the VA system revealed 73% of patients who reported TBI were also co-morbid for PTSD.[14] Whether this is actual diagnostic overlap or the result of poor instruments for differentiating the two entities remains a critical question for the Department of Veterans Affairs (VA). It is likely that both alternatives contribute to this situation. For example, several of the questions in the Clinician-Administered PTSD scale[15] identify symptoms that also could be a result of TBI, such as sleep difficulties, irritability, poor

concentration, memory difficulties, anhedonia, and social isolation. As an indirect consequence of this conundrum, patients in the VA system are often diagnosed with only one or the other, and the comorbidity is ignored.[12] Indeed, the VA admitted in November 2017 that it had misdiagnosed tens of thousands of veterans.[16]

Parsing out who has PTSD, who has TBI, and who has both is a critical issue for veterans. In the September 2015 issue of *Brain Imaging and Behavior*, a landmark paper on this question was published by a multi-center international team of clinician-scientists, including myself.[17] This group examined the neuroimaging data of 196 military and Veteran patients who had undergone SPECT imaging, which is a functional neuroimaging modality based on the intimate relation between neuronal activity and local oxygenated blood perfusion (the same principle upon which functional magnetic resonance imaging or fMRI is based). When the areas of the brain involved in the default mode network were examined, a striking difference emerged. TBI could be distinguished from PTSD using SPECT with 94% accuracy (sensitivity = 92%, specificity = 85%). In addition, the ability to distinguish PTSD from co-morbid TBI+PTSD was 92% (sensitivity = 87%, specificity = 83%).[17]

Identifying TBI or PTSD in an individual patient is of little help if there are no effective treatments available for TBI. This is where some of our revolutionary work is opening up new opportunity to potentially repair brain injury. A large body of research work in the healing properties of near infrared (NIR) light has been amassed over the past 30 years.[18] NIR laser therapy utilizes penetrating photonic energy in the infrared spectrum to induce physiological and biochemical changes within targeted tissues. Early work established that NIR delivered with a laser could speed wound healing,[19,20] induce stem cell proliferation,[21] and stimulate tissue repair in deep tissues, such as cardiac muscle.[22] NIR light of wavelengths between 600-1,200 nm[23] potently activate cytochrome *c* oxidase in the mitochondrial respiratory chain, which leads to increased adenosine triphosphate (ATP) production.[23,24] Furthermore, tissue culture and animal studies implicate secondary molecular and cellular events that appear to be activated NIR light in these wavelengths impinges on mitochondria. Furthermore, NIR light also has been shown to activate transcription in both the mitochondria[24] and the cell nucleus, with an increased transcription of over 100 genes,[24,25] including cell survival genes and key neural differentiation factors.[25] NIR light also increases the production of numerous growth factors and upregulates several inflammatory mediators in animal models.[26-28] Key growth factors stimulated by NIR light include nerve growth factor,[29] vascular

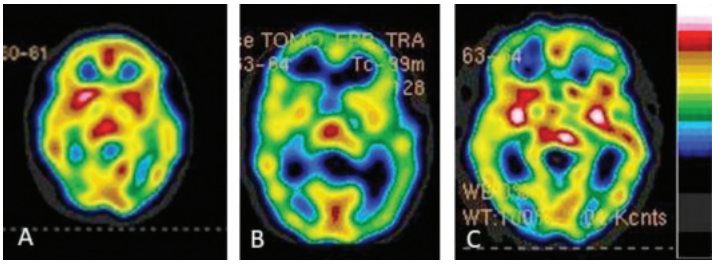


Figure 1. Cross sectional images from brain SPECT scans showing PTSD (A), TBI (B), and the combination of PTSD and TBI (C). Each has a very distinct appearance visually and when the default-mode network is analyzed, these conditions can be differentiated with 94% accuracy.[6]

endothelial growth factor,[30] brain-derived neurotrophic factor (BDNF),[31,32] and transforming growth factor-beta,[33] which may contribute to late brain remodeling after TBI.[18,24,26] For example, a fourfold increase in BDNF protein expression occurs in a mouse TBI model after 3 treatments with 810 nm NIR light.[32]

By using **multi-watt near-infrared laser therapy (NILT)**, we have shown the potential of coherent focused pulsed infrared light to provide superior penetration and focus in a controlled and safe manner to treat the living human brain. Patients have seen significant improvement of their symptoms, including: headaches, sleep disturbances, anxiety, mood regulation, impulsivity, depression, and resulting relationship problems and joblessness. The patients continue to do well after the treatment ends, even two to five years after receiving the treatment.

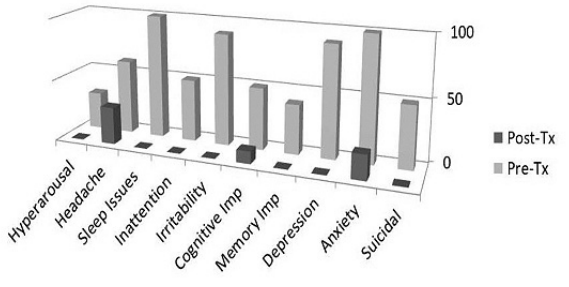


Figure 2: Summary of data from 10 patients treated with multi-watt NILT. Data showing changes in symptoms common to mild or moderate TBI. Many symptoms completely resolved. Headache persisted in 30% of patients, anxiety persisted in 20% and cognitive impairment persisted in 10% of patients.[26]

Our work with infrared light therapy shows it has benefit in PTSD and depression, as well. Our preliminary data on PTSD-related symptoms in our patients with TBI show a robust response.[26] We recently published our data on the impact of multi-Watt infrared laser on depression.[34]

DEMENTIA

Dementia actually encompasses several different diseases, including the well-known Alzheimer's disease (AZD), frontotemporal dementia (FTD), Lewy Body dementia, vascular dementia and the precursor condition – Mild Cognitive Impairment (MCI). Perhaps the earliest study of dementia, published by Bonte and colleagues in 1986, documented decreased temporal lobe perfusion in 37 patients with AZD using ^{133}Xe perfusion SPECT.[35] The early SPECT perfusion studies of AZD relied on a single-headed or low-resolution gamma camera.[36,37] Later studies utilized higher resolution gamma cameras; however, some groups still used inferior single-headed cameras which resulted in compromised data.[38] Processing and interpretation, like the equipment, have undergone remarkable progress resulting in significantly improved diagnostic accuracy. Early studies depended on visual subjective interpretation or "eyeballing". Inter-rater reliability was a significant factor.[39] Early attempts at semi-quantitative analysis remained subjective and compromised.[40-42] Notably, a weighted meta-analysis which excluded 123I-IMP and 99mT-ECD studies, derived a pooled weighted sensitivity and specificity of 48 99mT-HMPAO studies published prior to 2003. According to this meta-analysis, perfusion SPECT has a sensitivity of 74% and a specificity of 81% for the differentiation of AZD from elderly controls.[41] Studies encompassing the data published after 2003 showed considerably better accuracy.[43-46] Indeed, the combination of SPECT findings of temporal-parietal hypoperfusion and a clinical diagnostic profile consistent with AZD has a 96% sensitivity and an 84% specificity with even low-resolution single-headed SPECT cameras.[47] Taken together, studies of perfusion SPECT in the diagnosis of AZD with comparison to a longitudinal clinical course and/or histopathology demonstrates a sensitivity in the range of 82-96% and a specificity in the range of 84-89%.[46] This is comparable to the sensitivity of FDG-PET (88-94%) and superior to the specificity of FDG-PET (63-73%). See Figure 3 for an example of the typical appearance of FTD and AZD on perfusion SPECT.

The early pathophysiological changes which occur in AZD underscore the value of perfusion changes in the posterior cingulate as an early signal. The posterior cingulate gyrus receives input from the subiculum and projects to the anterior thalamus.[48] Several studies have demonstrated functional correlation between the posterior cingulate and the entorhinal cortex.[49,50] The entorhinal cortex appears to be one of the first sites to accumulate neurofibrillary tangles and neuritic plaques preceding even the hippocampus.[51] Indeed, portions of the entorhinal cortex may undergo 40-60% neuronal loss prior to measurable memory loss.[52] So, patients with only mild subjective memory impairment may already have significant AZD-specific pathology present in the entorhinal cortex. As a result, hypoperfusion in the posterior cingulate gyrus as revealed by a SPECT scan is a valuable early warning sign for AZD.[35,46] Indeed, SPECT perfusion scans are superior to FDG-PET scans in this area because the posterior cingulate gyrus has a higher baseline level of neuronal activity compared to the surrounding cortex.[46] Thus, FDG-PET may under-estimate the decrement in function in the key diagnostic area of the brain.

Recently, several groups have focused on novel methods of image analysis to enhance the identification of prodromal AZD among patients with MCI. Habert and colleagues[53] utilized statistical analysis in a sample of 83 patients with memory complaints who were followed over three years. They found similar sensitivity and specificity as described above. Pagani and colleagues[54] used principal component analysis to differentiate mild and moderate AD. Again, the hippocampus, parietal cortex, and posterior cingulate emerged as discriminative features for the severity of AZD. Chaves and colleagues[55] found linear kernel support vector analysis significantly increased the diagnostic power of SPECT in identifying early mild AZD. In a sample of 38 patients with

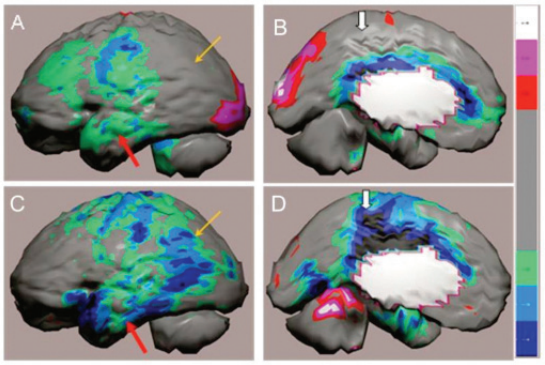


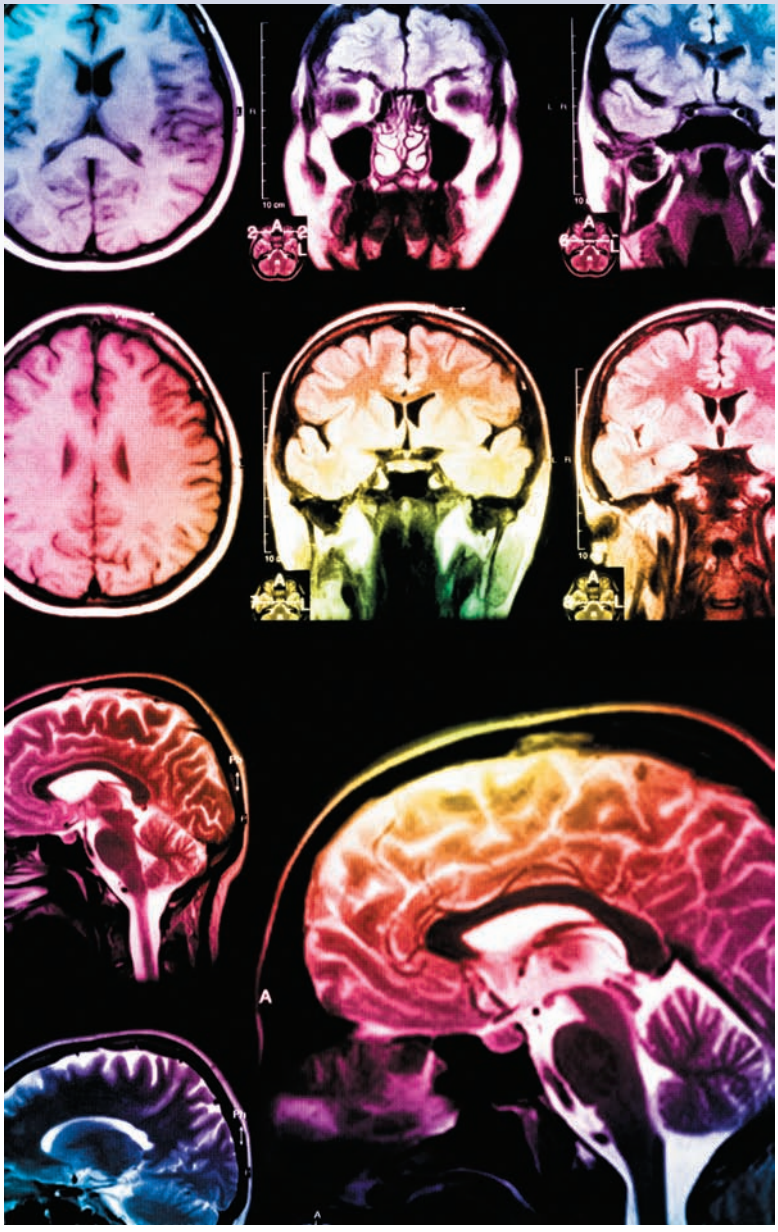
Figure 3: Figure 1. Tc-99m-HMPAO perfusion SPECT scan data from a patient with a diagnosis of fronto-temporal dementia (A,B) compared to the SPECT scan data of a patient with the diagnosis of Alzheimer's disease (C,D). The patients' data compared to a normative database (N= 68) and a map of statistically significant differences generated using the Oasis software by Segami Inc. Here, the color scale indicates gray for areas that do not differ significantly from the normative database. In contrast, areas of green, light blue and dark blue represent areas of more than 2, 3, and 4 SD below the mean perfusion of the normative database, respectively. Statistically significant increases in perfusion are illustrated in the red color scale. Decreased perfusion in the temporal lobes (red arrow), parietal cortex (orange arrow) and posterior cingulate gyrus (thick white arrow) are hallmark findings in Alzheimer's disease, but in frontotemporal dementia the posterior cingulate (thick white arrow) is preserved, but perfusion in decreased in the frontal and temporal lobes.

mild AZD, the approach yielded a sensitivity of 97%, a specificity of 100% and an accuracy of 99%.

In summary, SPECT is a valuable tool in the identification of AZD, the differentiation of other dementias, and the detection of MCI. In several studies, SPECT detected MCI functional patterns prior to the onset of significant neuropsychological impairment. SPECT out-performs clinical assessment alone which is generally 49-63% sensitive and 89-94% specific.[56] Even when using older, single-headed SPECT cameras and visual inspection, several studies have found SPECT can differentiate AZD with a sensitivity ranging from 82-96% and a specificity ranging from 84-89%.[46] This exceeds the standard set forth for minimal criteria for a biological marker of AZD as defined by the Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute on Aging Working Group57. Using sophisticated statistical analysis, perfusion SPECT scans can yield a sensitivity of 97%, a specificity of 100% and an accuracy of 99%.[55] SPECT, alone or in combination with genetic testing, has the potential to provide prognostic information and differentiate those at risk for progression of MCI to AZD.[46]

Currently, there are three amyloid PET tracers available. Each is priced at over $3,000 per scan. Regardless of the amyloid tracer, in healthy controls, the tracer uptake is limited to the white matter. The rim of uninvolved cortex can be clearly discerned in a normal amyloid scan. This is true until about age 50 years.[46] At this point, roughly 10% of controls will show cortical uptake. Persons in their 60's will show cortical uptake in 12% of cases.[46] This false positive rate increases to 30% for patients in their 70's and 50% in patients in their 80's.[46] So while amyloid scans have a certain sex-appeal and have been heavily promoted by the manufacturers, they have declining specificity with age. This, combined with the cost and the fact that many insurance companies and US Medicare will not reimburse for the procedure, lessens the appeal of amyloid scans. In contrast, SPECT scans for dementia workup are reimbursed by Medicare and many insurance companies.

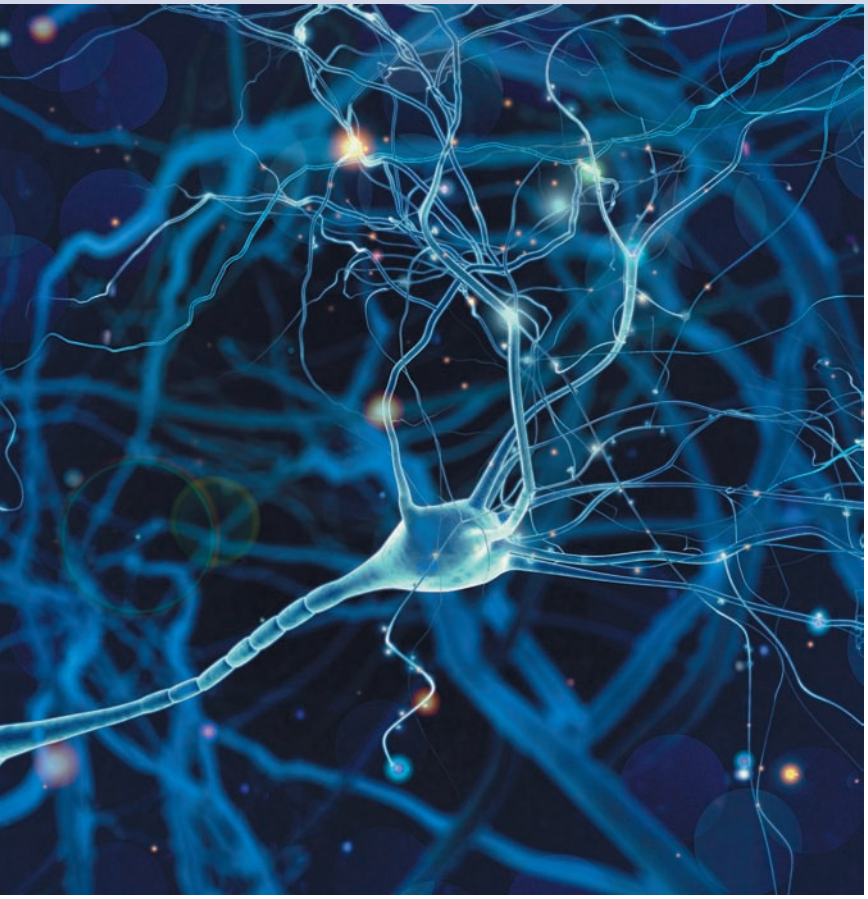
Over the next 15 years, the number of patients with AZD will almost triple worldwide. The population affected by MCI will grow to at least 123 million.[46] As disease mitigating pharmaceuticals become available, early identification of patients with MCI who are likely to benefit will emerge as a critical need. Interrupting the swelling ranks of those affected by AZD will require early diagnosis of MCI and differentiation of those likely to progress and those who are stable. Research presented above demonstrates that SPECT with



statistical parametric analysis can distinguish subtypes of MCI with reasonable accuracy. While the goal for the diagnosis of AZD has been 100% accuracy, this reflects the concern of giving an incorrect diagnosis. As our ability to pharmacologically alter the course of these disease processes improves, the burden is shifted to providing an early preliminary diagnosis so that treatment can be initiated early while mitigation of the disease process is still possible. Newer high resolution, low radiation dose, SPECT cameras are on the horizon, which will further lower the risk of early diagnosis by SPECT. SPECT can provide an economical strategy for early identification and monitoring.

PSYCHIATRIC CO-MORBIDITY

Psychiatry and Neurology are fields of medicine rooted in the brain. While Freudian musings about the impact of childhood experiences on



the development of Id and Ego can be entertaining, ultimately the mechanism by which these childhood experiences influence the adult are by changes in the functional neurocircuitry and neurophysiology. The interplay of genes and experience take place on the canvas of neurocircuitry. Neuroimaging has found an uneasy alliance with Neurology. However, Psychiatry has rebuked neuroimaging. While there was initial excitement in Psychiatry about CT imaging and it was employed at multiple centers to search for structural abnormalities in a variety of psychiatric conditions.[58] When MRI became widely available, with its greater resolution and improved white matter/grey matter distinction, a renewed effort to find anatomical correlates for psychiatric conditions was launched.[59,60] These efforts proved relatively fruitless. Since anatomy tells us little about ***brain function***, CT and MRI fell to the wayside in Psychiatry.

First, it is important to make a distinction between the idea that neuroimaging can reveal what is going on in the brains of patients with various disorders and the idea of neuroimaging providing us with a "fingerprint" or pathognomonic sign of a Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnosis. Let me remind you that DSM diagnoses were developed as a tool to categorize patients by their signs and symptoms – their subjective experiences and some objective signs of their behavior. The DSM was not designed with the brain in mind. There is little or no reason to assume that the functional aspects of the brain will neatly fit into DSM categories. Secondly, there is an assumption in Psychiatry that patients have only one diagnosis – a misapplication of Occam's (Ockham's) razor. Indeed, according to DSM criteria, if a person has ADHD and another DSM diagnosis, they technically cannot have ADHD. Yet, clinically we know that comorbidity is the rule rather than the exception in ADHD. Similarly, patients with depression often have comorbid anxiety. More than likely, we will find that patients will have multiple processes co-occurring. Third, there is an expectation of neuroimaging to perfectly "make the diagnosis", which is perhaps at the heart of the somewhat irrational attacks made by psychiatry upon neuroimaging, often from a position of ignorance. It does not seem that Psychiatry exercises similar scrutiny in examining the diagnostic accuracy of thyroid tests, Conners' Continuous Performance Tests, Minnesota Multiphasic Personality Inventory (MMPI), Rorschach's, chest X-rays, cholesterol tests, or a host of other modalities with use in the practice of medicine. For example, we routinely use chest X-rays to diagnose various disorders. There is an assumption that chest X-rays give us the diagnosis. Let's take the example of a large solitary pulmonary mass of size greater than 4 cm. According to Reeder and Felson's definitive text Gamuts in Radiology (1975),[61] this could be an abscess, bronchogenic carcinoma, alveolar cell carcinoma, metastasis, arteriovenous malformation, bronchial adenoma, fluid filled cyst, hamartoma, hematoma, inflammatory pseudotumor, organized nodular pneumonia, lipoid pneumonia, loculated pleural fluid, lymphoma, pneumoconiosis, pulmonary sequestration, sarcoma, or Wegener's granuloma. How does one distinguish among this myriad of diagnostic possibilities? It is done by clinical correlation and additional testing. The diagnosis is made ultimately by the physician as a result of synthesizing the imaging data, the testing data, and the clinical information. PSYCHIATRY IS, AND SHOULD BE, NO DIFFERENT. Our diagnoses should be made based on the synthesis of data – laboratory data, neuroimaging data, and clinical data. But ultimately, the physician makes the diagnosis, not the lab test. Outside of bacterial cultures, there are very few tests with 100% sensitivity or specificity.

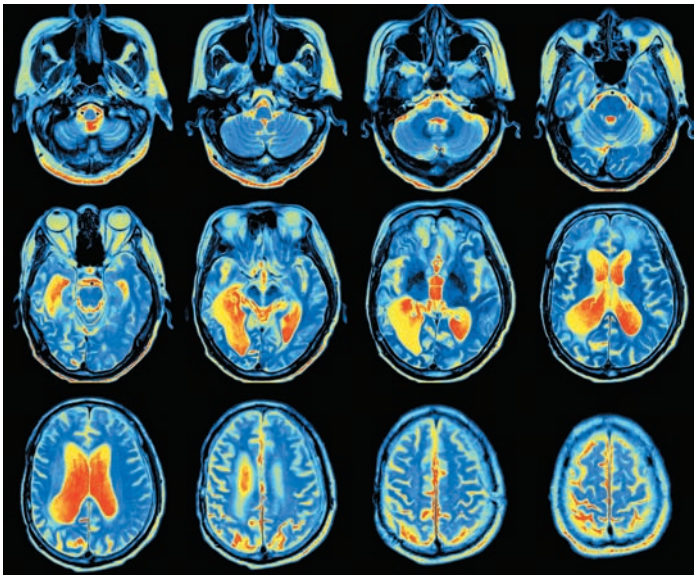
Let's take the example of ADHD. Many believe you can diagnose ADHD from the door or down the aisle of a grocery store wherein a child is running about uncontrolled. However, let's example the specific diagnostic criteria for

ADHD – restlessness, hyperactivity, poor concentration, distractibility, and inattention. As shown in the chart below, these supposedly diagnostic criteria overlap with numerous diagnoses, including generalized anxiety disorder (GAD), mania, irritable depression, conduct disorder/oppositional defiant disorder (CD/ODD), and traumatic brain injury (TBI). With functional neuroimaging, certain neuro-physiological processes become evident which guide the diagnosis. In a neurotypical person, frontal lobe activity increases during concentration. In persons with ADHD, frontal lobe activity actually decreases when they concentrate. It is hard to focus because the frontal lobes – specifically the orbitofrontal cortices - go "offline" when they attempt to concentrate due to a deficiency in frontal lobe dopamine.[62] I have seen many cases of adolescents with "Bipolar disorder" who are not responding to mood stabilizers, like lithium or valproate, who show frontal lobe decrease with concentration. Not surprisingly, they do quite well on a stimulant medication. Cherkosova and Hechtman[63] reviewed the neuroimaging findings in ADHD in the Canadian Journal of Psychiatry in 2009. The frontal lobes and the connection between the striatum and frontal lobes figure prominently in the research literature. Surprisingly, the cerebellum has an important role in ADHD affecting error frequency and response to stimuli. There are possibly multiple "forms" of ADHD, as some patients show abnormal temporal lobe or abnormal parietal lobe function. Recently, Schneider and a group of Canadian clinicians[64] examined the contribution of orbitofrontal cortical hypoperfusion in the diagnosis of ADHD. They found that reading only conventional tomogram or "slice" data resulted in low sensitivity (4%) and low positive predictive value (44%). In contrast, using 3-dimensional renderings of the SPECT data increased sensitivity and positive predictive value (84% if the concentration scan was used).

	ADHD	GAD	Mania	Depression	CD/ODD	TBI
Restlessness	x	x	x	x		x
Poor Concentration	x	x	x	x	x	x
Increased motor activity	x	x	x		x	x
Distractibility	x	x	x	x	x	x
Irritability			x	x	x	x

SPECT functional neuroimaging also guides the clinician away from an erroneous diagnosis of ADHD. For example, when there is no sign of orbitofrontal hypoperfusion during a concentration task and the entire cortex is quite overactive, one can feel secure in diagnosing mood dysregulation and treating with a mood stabilizer. I have also observed numerous cases of learning disorders in which the only area of abnormal function with markedly decreased temporal lobe function. For example, one young adolescent girl who was quite bright and articulate, but had math comprehension at the 35th percentile and reading comprehension at the 10th percentile. Her Connors Continuous Performance Test was negative for ADHD. She had very low temporal lobe function. As I have done for many such cases, I started her on donepezil, a medication used in treating Alzheimer's disease which increases acetylcholine levels. Since acetylcholine is the neurotransmitter of learning and memory and a key neurotransmitter of the temporal lobes, it is not surprising that within three months, her math skills had jumped 2 years and her reading comprehension had jumped 1.5 years.

SPECT functional neuroimaging can show other causes of cognitive dysfunction. I have now seen several cases of Chronic Fatigue Syndrome which presented as predominately academic struggles. The SPECT scan did not show frontal lobe hypoperfusion; rather, it showed diffuse hypoperfusion involving the entire brain. Additional laboratory testing confirmed the presence of viral causes of Chronic Fatigue Syndrome and the patients' academic struggles improved after treatment with antiviral therapy.[65] TBI also is often confused with ADHD, depression, anxiety, and other psychiatric diagnoses. TBI, due to damage to different functional areas in the brain, can present with a myriad of symptoms, including poor concentration and focus. Stimulants can be helpful in TBI because they increase frontal lobe dopamine, but they are a bandaid, not a treatment. As described above, treating the TBI with NILT has resulted in substantial improvement in concentration and cognitive performance for many patients.



CONCLUSION

Perfusion SPECT functional neuroimaging can teach us much about a patient's brain. The challenge that psychiatrists face is to correctly understand the strengths and weaknesses of the diagnostic constructs and how data on brain function fits together with clinical information. The false expectation of precise or pathognomonic symptoms or signs leads to unrealistic expectations from functional neuroimaging – be it SPECT, functional MRI, or FDG PET. I have offered numerous examples of situations in which the symptoms do not match the diagnosis – depressive symptoms in TBI, dementia symptoms can be either AZD or FTD, and ADHD symptoms in a variety of conditions. Information from functional neuroimaging can yield a better diagnosis and speed the diagnostic process.[64] Perhaps with these thoughts both psychiatrists and nuclear medicine physicians will reconsider their biases against perfusion SPECT neuroimaging. Decades of research with functional MRI have failed to yield any useful clinical algorithms. In contrast, SPECT has demonstrated sensitivity/specificity in the 85-95% range for TBI, PTSD, AZD, FTD, MCI, and offers relevant insight into alternative neurological processes responsible for symptoms such as depressed mood, impulsivity, executive dysfunction, and others. ■

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Dr. Howard Chertkow, MD,
Director of the Jewish General Hospital/McGill Memory Clinic
Montreal, Canada

360 RESEARCHERS FIGHT AGAINST DEMENTIA

CANADIAN CONSORTIUM ON NEURODEGENERATION IN AGING

By Fadwa Lapierre

Two heads are better than one. This well-known saying applies more than ever to the creation of the new Canadian Consortium on Neurodegeneration in Aging (CCNV), which brings together over 300 researchers across the country.

The aging of the population is doing its work. In a few years, 20% of the Canadian population will be elderly. Dementia, a real public health problem, is closely linked to this. In 2011, there were an estimated 747,000 Canadians with dementia, which is expected to double in the next 20 years!

"The tsunami of dementia is falling on our society; a large wave of patients is expected in the coming years. The only way to counter this is to put major efforts into research," says Dr. Howard Chertkow, Scientific Director of the CCNA, cognitive neurologist and co-founder and Director of the Jewish General Hospital/McGill Memory Clinic.

The CCNA is funded with $31.5 million over five years by the Government of Canada through the Canadian Institutes of Health Research and a group of 13 public and private sector partners, including the Alzheimer Society of Canada and the Canadian Institutes of Health and the Fonds de recherche du Québec – Santé. An additional $24 million is also invested by a sub-group of partners in Ontario and Quebec.

"Canada has found a cure for diabetes, perhaps we will be the next to find one for dementia? On the one hand, the population with dementia increases, on the other hand, research on the brain is still early. It's an international emergency, governments are starting to realize the costs to society if we do not find a cure quickly," says Dr. Chertkow.

Let's keep in mind that dementia would cost the country's economy nearly $33 billion a year, including the direct medical and indirect costs of lost income.

The role of the Scientific Director is to manage the teams and ensure that they have the resources and infrastructure to achieve their goals. "Normally a researcher will work alone," says Dr. Chertkow. In this issue, everyone understands that it is better to work on a national team, in order to benefit from everyone's knowledge. There is a high level of cooperation and synergy in Canada, sometimes better than elsewhere. We share our information. We need renowned researchers in their field to find answers."

The 20 research teams will focus on three themes:

- primary prevention: prevent the disease from occurring
- secondary prevention: delay or slow down the clinical progression of the disease
- improve the quality of life for Canadians living with these diseases and the people who care for them

Research initiatives range from molecular genetics to the organization of health systems. For example, a cohort of 1600 people with different types of dementia will be observed. First nations dementia, which is three times higher than in the general population, or the technological approach to developing a smart home that would allow patients to stay at home is also the subject of research.

Dr. Chertkow remains confident of the important progress that the CCNA will make possible. "The future is not clear, we do not know how close we are to a solution. Will we find a cure in two years, five years or 25 years? One thing is certain, joint efforts will enable us to better understand the disease and its causes, test new treatments and improve the quality of life of patients and their families. These researchers are working hard to find a cure for neurodegenerative diseases."

CCNA's head office is located at the Lady Davis Institute of the Jewish General Hospital in Montreal. ■

* Figures and statistics are from the Canadian Institutes of Health Research

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Nathan Hermony
Global Manager, Nuclear Medicine
Business Leader at General Electric
Haifa, Israel

Interview with: Nathan Hermony

As a "nuclear" engineer, you have witnessed many changes in the world of nuclear medicine over the past few decades. What are the key landmarks that you have seen over the past 30 years in term of gamma cameras?

I believe that main landmarks are clearly the move from planar to SPECT including Dual detectors, but there are two main landmarks that we believe changed and continue to change the way SPECT is being used. The first one is the introduction of Hybrid SPECT/CT systems in 1999, when we introduced the first SPECT/CT in the world, the Hawkeye, which was later followed by others with improved CT.

The additional CT that brings the anatomy together with function, improved significantly image quality by performing AC (Attenuation Correction) and the ability to localize the lesion (moving from Unclear Medicine to New Clear Medicine). Once introduced, it was shown that it changed in more than 35 % patient management. It also enabled one of the most important recent trends to bring quantitation to enable better, more accurate and precise diagnosis.

The second major development that we have seen recently is the introduction of solid state detectors like CZT. This enables a much lesser dose to the patient, and/or, much lower acquisition time. We currently see doses and acquisition time going down by factor of 4 to 5 time of a conventional camera. But it also enables dynamic SPECT to measure blood flow. With the great energy resolution and spatial resolution, it enables to image simultaneous multiple isotopes to improve specificity, accuracy while improving efficiency.

Personalized medicine, molecular imaging and treatment targeting are becoming an integral part of the practice of medicine. How do they affect the vision and strategies of GE for NM equipment?

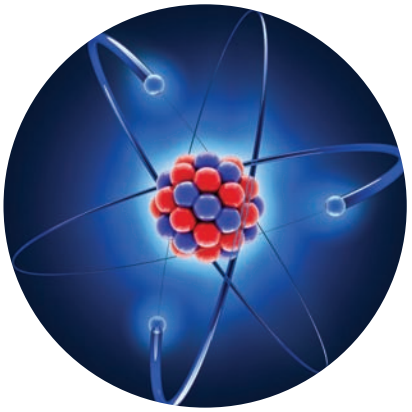
It is clear that the Theranostic (Therapy together with Diagnosis) is already becoming the way Nuclear Medicine Physician will help patients. We, at GE, have developed quantitative tools for treatment planning as well as treatment follow-up. We are already working with research sites on Treatment planning and optimization per patient of LU177 for Prostate Cancer treatment. We also developed tools for surgeons to help in planning lung resections based on the CT and the SPECT. We launched Brain quantitation for Brain perfusion for different indications like epilepsy, TBI, etc. We clearly believe that quantitation is the future.

What do you see as main innovations in nuclear medicine in the next ten years?

I believe that we will see more intelligent scanners with improved workflow of patients in the department and significant improvements in resolution and sensitivity. This, together with Artificial Intelligence, will help in more accurate diagnosis.

GE has been a great supporter of educational initiatives. To your opinion, what role do you see the Pangea-ePatient magazine play for nuclear medicine practice?

Education is key in improving the utilization of SPECT and PET. We clearly believe that Molecular Imaging is underutilized and as we and you believe, SPECT and PET are an imaging that clearly demonstrate any disease much earlier than any anatomy imaging. We believe that Pangea-ePatient should reach out to patients and referral physicians to educate and increase awareness of the MI modality of the advances that were in equipment and mainly the reduction of radioactive dose and the improved sensitivity in detecting disease and its specificity. ■



Dr. Sonia Neubauer, M.D.
Director Nuclear Medicine Dpt.
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Santiago, Chili

¿MARIHUANA INNOFENSIVA?

La tendencia mundial a legalizar la marihuana ha causado una disminución de la sensación de que se trata de una droga dañina, un aumento del consumo y un inicio en adolescentes cada vez a menor edad. Esto ha causado un aumento en las consultas por complicaciones de su uso como falta de motivación (el síndrome amotivacional), bajo rendimiento académico, crisis de pánico, accidentes y aparición de una esquizofrenia en sujetos predispuestos.

En Medicina Nuclear contamos con el NeuroSPECT, un examen que muestra en una imagen tridimensional el flujo sanguíneo a las células del cerebro (la perfusión cerebral), lo que representa el funcionamiento de las distintas áreas cerebrales. Para facilitar su interpretación, voluntarios sanos se sometieron al NeuroSPECT con Tc99m-HMPAO para crear bases de datos normativas por grupo de edad. Al comparar la perfusión cerebral de cada paciente con la de sanos de su grupo de edad, es posible destacar las áreas que funcionan muy diferente en el enfermo, expresado en desviaciones standard del promedio de lo encontrado en los sanos.

Esta técnica es útil en diversas enfermedades neurológicas y psiquiátricas como por ejemplo en el diagnóstico de demencia, epilepsia, trauma encefálico, exposición a sustancias neurotóxicas (como alcohol, drogas ilícitas, pesticidas, solventes, etc.), enfermedad vascular cerebral, encefalomielitis miálgica/síndrome de fatiga crónica, déficit atencional, trastorno bipolar, esquizofrenia, depresión, trastorno obsesivo-compulsivo, síndrome de stress post-trauma y estudio de respuesta a tratamientos.

Un estudio en escolares consumidores exclusivamente de marihuana al menos hace 18 meses y con consumo cuatro veces en el mes previo, muestra en test psicológicos un significativo deterioro en la memoria, atención, concentración, organización y capacidad de planificación cuando se los compara con sus pares que no consumen drogas.

Se puede ver la comparación entre un NeuroSPECT normal (figura 1) y un NeuroSPECT de un escolar consumidor de marihuana estudiado en un día normal de clases (figura 2). Se muestra en color gris las áreas del cerebro con perfusión en el rango del 95% de los voluntarios sanos (± 2 desviaciones standard del promedio normal). En el normal predomina el gris y existe aumento de la perfusión cerebral en colores rojo, rosado y blanco por activación fisiológica de la corteza visual occipital durante el examen (posterior view). En el escolar consumidor de marihuana hay múltiples áreas de marcada disminución de la perfusión, especialmente severo en lóbulos temporales (incluye el hipocampo) en colores celeste, azul y verde a más de dos, tres y cuatro desviaciones standard por debajo del promedio de los normales respectivamente, o sea son áreas con significativa menor perfusión (que funcionan menos). El NeuroSPECT de todos los escolares consumidores de marihuana mostró múltiples áreas desorganizadas de disminución marcada de la perfusión cerebral, especialmente en áreas relacionadas con el ánimo (área 25 de Brodmann), con las funciones ejecutivas (áreas 10 y 11 de Brodmann) y con las habilidades cognitivas (lóbulos temporales, hipocampo) coincidiendo con los test psicológicos. Una imagen dice más que mil palabras.

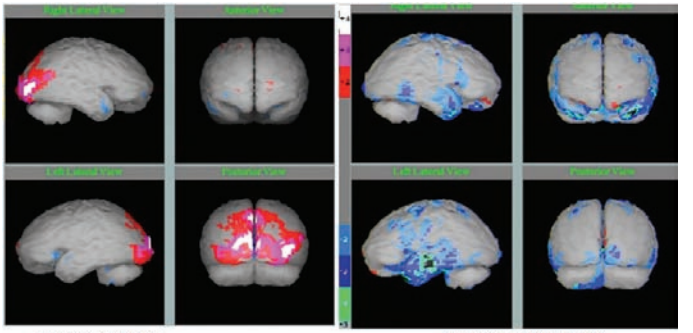


FIGURA 1 : SANO FIGURA 2 : MARIHUANA

El NeuroSPECT confirma que la marihuana no es inofensiva.

Dr. Jun Hatazawa, M.D., Ph.D.,
President of the AOFNMB, Japan

NUCLEAR BRAIN IMAGING IN MEDICAL PRACTICE IN JAPAN

BASIS OF NUCLEAR BRAIN IMAGING

Brain is an organ by which we can perceive, exercise, learn, remember, think, behave and imagine among other tasks. To fulfill its functions, the brain exclusively metabolizes glucose to produce energy in the form of adenosine triphosphate (ATP) by oxidative glycolysis. Half of the ATP is used for the electrical activity of the neurons, and the other half is consumed for the synthesis and catalysis of brain tissue components. ^{18}F fluoro-deoxy-glucose (^{18}F FDG) PET imaging (figure 1) demonstrates very nicely the that that the human brain consumes more glucose than any other organ of the body. The human brain consumes approximately 100-150g of glucose per day.

Brain function is maintained by a continuous supply of glucose and oxygen by the cerebral circulation. The Cerebral Blood Flow (CBF) is tightly controlled to supply the brain with the necessary amount of glucose and oxygen needed to perform its functions. Over the past few decades the scintigraphy mapping of the CBF has been used to determine and evaluate the activation of the different areas of the brain while performing various tasks such as speech, calculation, memory, and exercise (figure 2).

Figure 1

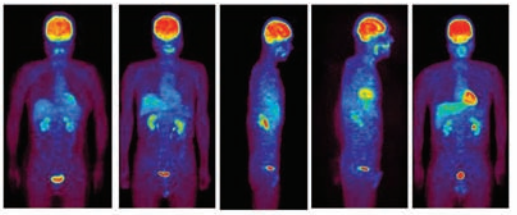


Figure 1. Whole body PET images 1 hour after intravenous administration of F-18 fluoro-deoxy-glucose (FDG) in five different normal volunteers. All subj showed high FDG uptake to their brain. Myocardial uptake was found when blood glucose level was high. FDG is excreted from urinary system.

Figure 2

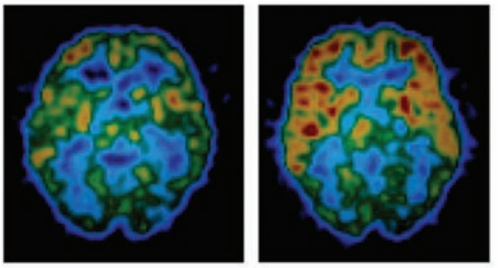


Figure 2. Tomographic FDG PET images in single normal volunteer. Left imag was obtained under resting condition during any specific thinking. Right imag was obtained under resting condition during imagining bright future of life. Positive thinking was associated with bilateral frontal lobe activation.

BRAIN STROKE

Brain is very sensitive to CBF reduction because of the need of a continuous and uninterrupted supply of glucose and oxygen. Brain perfusion imaging in nuclear medicine is now employed to detect CBF change in central nervous system diseases. Stroke is the most common neurological disease in adults and can be fatal. In acute ischemic stroke due to embolic occlusion of carotid artery or major cerebral arteries, CBF suddenly decreases to less than 50% of normal level. Patients complain of difficulty of motion, sensory loss, and finally consciousness disturbance. Even in such situation, the brain can still extract glucose and oxygen as much as possible from decreased CBF, and can survive during 6 hours of onset (figure 3). If the blood clot is resolved within 6 hours of onset, recirculation can minimize ischemic brain damage or rescue completely without any neurological symptoms (figure 4).

In chronic ischemic stroke due to atherosclerotic stenosis of major cerebral arteries, CBF is gradually decreased. Patients first complain of transient motion and/or sensory disturbance for several minutes once a month, followed by more frequent onset and longer duration. It indicates high probability of impending

Figure 3

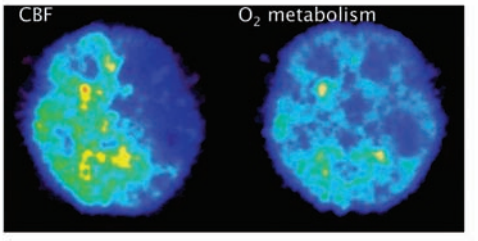


Figure 3. Cerebral Blood Flow (CBF) (left) and Cerebral Oxygen Consumption (right) in a patient with acute embolic occlusion of left internal carotid artery s within 6 hours of onset. CBF and oxygen consumption was measured by inhala of $C^{15}O_2$ and $^{15}O_2$, respectively. CBF was decreased to less than 50% of Contralateral hemisphere, but oxygen metabolism was maintained.

Figure 4

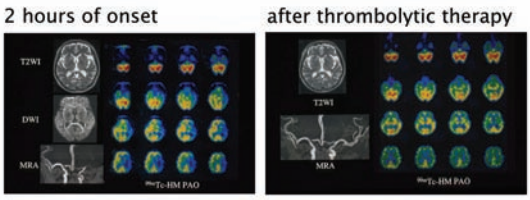


Figure 4. This patient showed sudden onset of right hemiparesis and consciousn Disturbance. MRA indicated left middle artery occlusion without any signal chan MR T2WI and diffusion weighted images 2 hours of onset. 99mTc-HMPAO SPEC brain perfusion imaging showed 50% reduction of CBF. Acute thrombolytic thera by recombinant tissue plasminogen activator resulted in immediate recanalizati recovery of CBF without ischemic brain injury.

Figure 5

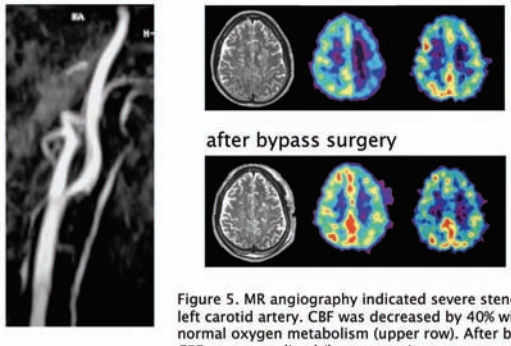


Figure 5. MR angiography indicated severe stenosis of left carotid artery. CBF was decreased by 40% with normal oxygen metabolism (upper row). After bypass, CBF was normalized (bottom row).

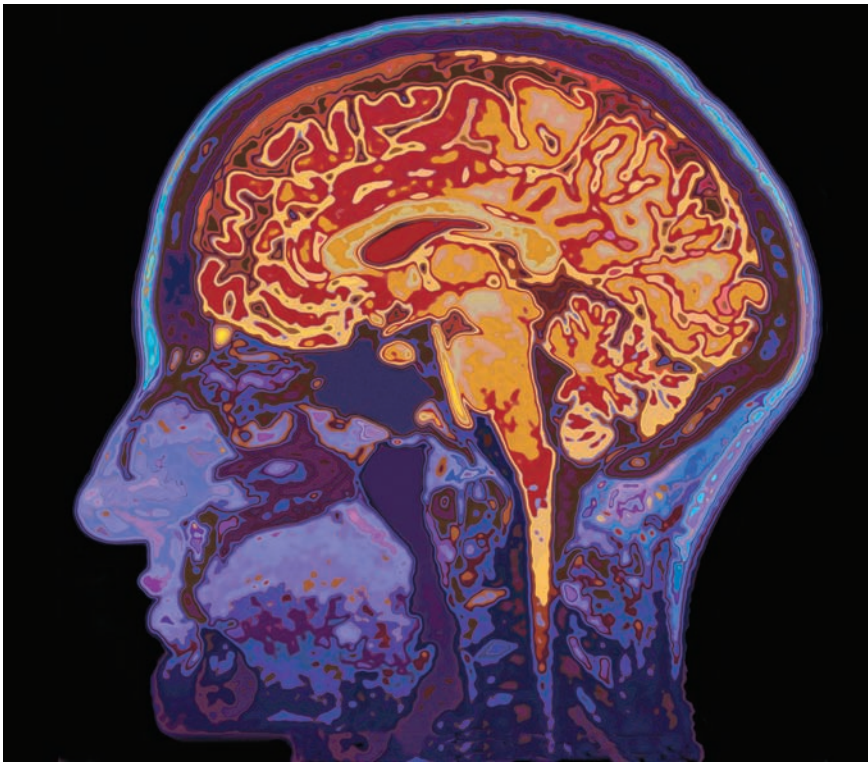
cerebral infarction with irreversible neurological deficits. Brain perfusion SPECT provides information on the severity of circulation disturbance before the onset of cerebral infarction and a guide for therapy strategy such as interventional reconstruction of stenotic artery, surgical removal of atheroma in thick arterial wall, or extra cranial-intracranial bypass surgery (Figure 5).

EPILEPSY

Epilepsy is one of the major neurological diseases in children. Most patients are treated with anti-epileptic medications, but around 10% of epileptic children needs further treatment such as surgical removal of epileptogenic foci. During epilepsy, epileptogenic lesion shows abnormally increased CBF. Brain perfusion SPECT is employed to localize epileptogenic foci in patients with intractable epilepsy for surgical removal (Figure 6).

ALZHEIMER'S DISEASE

While aging, people experience forgetfulness. At the very early stage of Alzheimer's disease (AD), patients complain of memory impairment. It is difficult to distinguish Alzheimer's symptoms from physiological forgetfulness. Brain Perfusion Imaging in patients with cognitive impairment is now employed to categorize among AD, frontotemporal dementia, dementia with diffuse levy body disease, and other types (figure 7). Histopathological prediction of CNS diseases using PET/CT is now extending to Alzheimer's disease where β-amyloid and tau protein deposition is visualized.



PARKINSON'S DISEASE

Brain functions require the sophisticated integration of neuronal signals among population of neurons. Communication among neurons is done by releasing chemical compounds called neurotransmitters released by a neuron and binding to another. Neuron to neuron communication failure happens due to neurotransmitter "dopamine" deficiency in Parkinson's disease (figure 8), "acetylcholine" deficiency in Alzheimer's disease, and "serotonin" deficiency in major depression. DatSCAN is a new SPECT tracer that enables the diagnostic of Parkinson's disease (see Dr. Christian Scheiber article in this issue).

Figure 6

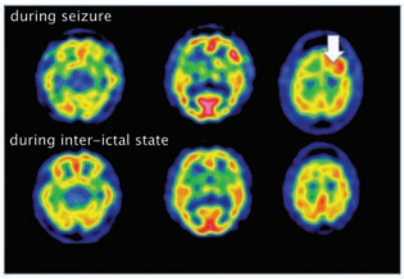


Figure 6. Tc-99m ECD brain perfusion imaging in a patient with intractable epilepsy. Upper row images were obtained during seizure, and bottom row images were obtained during no seizure confirmed by electro-encephalograph The arrow indicates increased CBF during seizure indicating epileptogenic focus.

Figure 7

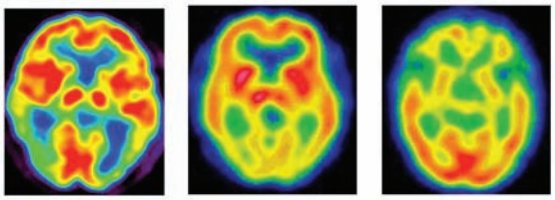


Figure 7. In patients with cognitive impairment, regional reduction of glucose metabolism is a diagnostic marker of Alzheimer's disease (left, temporal lobe diffuse Levy body disease (center, temporal lobe and occipital lobe), and fron temporal dementia (right, frontal lobe and temporal lobe).

Figure 8

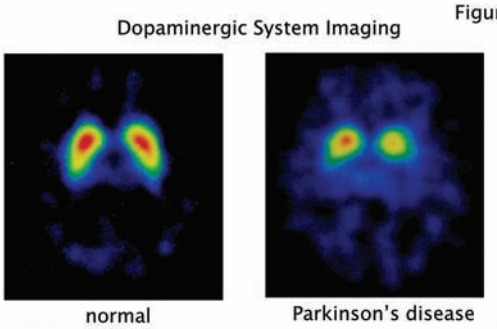


Figure 8. ^{123}I–β–CIT SPECT images in normal subject (left) and in a patient with Parkinson's disease (right). Reduction of ^{123}I–β–CIT indicated a failure o dopaminergic signal transduction from substantia nigra to putamen in Parkinson's disease (right).

BRAIN TUMOR

Brain tumor is one of the most dreadful diseases in adults and children. The therapeutic strategy is usually determined by histo-pathological classification according to World Health Organization grading. Biopsy of brain tumor is invasive because of transcranial tissue sampling. ^{18}F-FDG or ^{11}C-Methionine PET/CT is an alternative way to evaluate, non-invasively, the histopathological malignancy of cerebral gliomas non-invasively (figure 9).

NUCLEAR BRAIN IMAGING IN JAPAN

In Japan, one million and eighty thousand nuclear medicine studies are performed every year (National Survey of Nuclear Medicine Practice, Japan Radioisotope Association) using single photon isotopes on planar and SPECT cameras. Two hundred and fifty thousand of these studies, i.e. 22% are for brain imaging. Ischemic stroke, Parkinson's syndrome, cognitive impairment, epilepsy, head injury (especially after traffic accident), and brain tumor are the major indications. The cost of the study is approximately $400~500 US. Our national insurance system covers 70% of the cost and patients pay about 30%.

BONE SCINTIGRAPHY (30%) AND MYOCARDIAL PERFUSION IMAGING (22%)

Compared to other countries and other nuclear medicine studies (bone scintigraphies and cardiac studies represent 30% and 22% respectively), in Japan is the availability and the widespread use of dedicated brain SPECT software such as eZIS (Dr. Hiroshi Matsuda and his colleagues) and iSSP (Dr. Satoshi Minoshima and his colleagues). In patients with cognitive impairment, hypo-perfusion is detected on a pixel-by-pixel and compared to a normal data base (Figure 10). It is objective, comprehensive, and reproducible for nuclear medicine physicians, referring doctors, and patients.

CONCLUSION

Nuclear brain imaging with SPECT and PET in Japan is a significant part of the nuclear medicine practice. It is applied to various brain disorders to detect physiological and metabolic abnormality before morphological changes become evident. The availability and use of performant and reliable analytical software is a significant factor for the success of brain imaging.

Figure 9

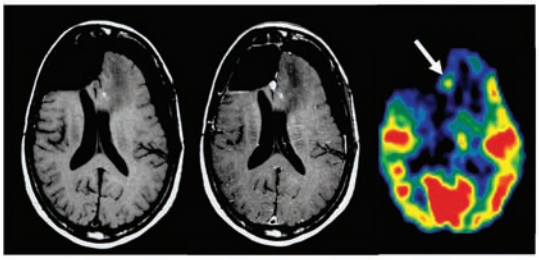


Figure 9. Non–contrast (left) and contrast (center) MR images and FDG PET image (right) after surgical removal of cerebral glioma. Small nodule located in resection border showed high uptake of FDG indicating residual tumor.

Figure 10

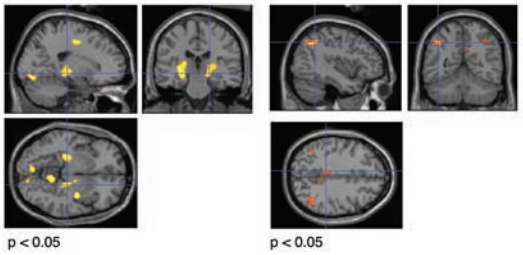


Figure 10. Statistical parametric analysis of forgetfulness (left) and Alzheimer' disease (right) by SPECT brain perfusion imaging. Forgetfulness showed bilate hippocampal hypoperfusion, while Alzheimer's disease showed hypoperfusion bilateral parietal lobes, posterior cingulate gyrus, and precuneus.

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Nicolas Rondeau Lapierre
Directeur marketing
Les éditions Multi-Concept inc.
Social media consultant

Nuclear Medicine Social Community Communication Tool: Coming soon

In the upcoming issue of the ePatient, we will be discussing strategies and new techniques available in social networks to promote and expand nuclear medicine beyond physical borders. This new segment will demonstrate practices used in everyday instances, which can be easily integrated into a digital marketing plan using social media tools and components.

Interview with: Dr. Yaming Li, President of the Chinese Society of Nuclear Medicine

China is the most populated country on Earth. For most of us, it is difficult to imagine how the Chinese population can access the nuclear medicine services that the Chinese patients need. Can you give our readers a synopsis of the status of nuclear medicine services across China and the role that the Chinese Society of Nuclear Medicine plays to promote nuclear medicine in China?

Nuclear medicine started in China in the 1950s. After 60 years of development, nuclear medicine has become an important part of medicine and an independent department in most hospitals in China. In the last decade, departments of nuclear medicine were established in most municipal hospitals. Even some developed-county level hospitals can provide nuclear medicine services nowadays. The services provided by nuclear medicine include in vivo imaging (PET/CT, PET/MRI, SPECT/CT, and SPECT), radionuclide therapy (out-patient and in-patient services) and in vitro analysis. According to the national survey of nuclear medicine in 2016, there are 891 departments of nuclear medicine, 246 PET/CT scanners, 6 PET/MR scanners, 774 SPECT/CT (or SPECT) scanners, and 101 cyclotrons, 1832 beds for radionuclide therapy. In 2016, about 500,000 PET/CT studies were performed (86.9% on oncology, 0.8% on cardiac and 2.7% neurology, respectively). About 2.1 million SPECT and SPECT/CT studies were performed (top 5 of SPECT/CT or SPECT studies were bone imaging, thyroid imaging, renal function imaging, cardiac imaging and I-131 imaging, respectively). Approximately 0.6 million cases of radionuclide therapy were performed (including 0.17 million cases of hyperthyroidism, 0.15 million cases of applicator therapy, and 60,000 cases of DTC).

Chinese Society of Nuclear Medicine (CSNM) was established in the 1980s. The regular term of service is 3 years. It is now the 11th committee, and there are 11 study groups under the branch of Nuclear Medicine. They are oncology group, PET group, cardiology group, neurology group, radiopharmacology group, science and education group, foreign exchange group, functional imaging group, treatment group, and so on. CSNM devotes itself to many different fields, including popularization, technology promotion and academic communication of nuclear medicine; constituting guidelines and standardizing clinical use of nuclear medicine; serving as counsellors for the government administrations on policies and regulations related to nuclear medicine; proposing advices to the related government administrations about how to develop nuclear medicine. Due to the great efforts of CSNM, the related Chinese government administrations have paid more and more attentions to nuclear medicine, and formulated a series of policies to guarantee the healthy development of nuclear medicine. CSNM holds annual meetings every year. In the 2017 annual meeting, there were over 1500 participants. Each study group also organizes academic activities on ana annual basis. In addition, nuclear medicine branches of provincial medical association have been set up and a variety of academic activities were organized annually. In recent years, in response

to the government's new health care reform to build a new type of medical system with "serious illness should be treated within the county", CSNM proposed the development strategy of "one nuclear medicine department for one county" and established new nuclear medicine department in county-level hospitals in many provinces in China. The establishment of nuclear medicine departments in county-level hospital will usher in a new and rapid development opportunity for nuclear medicine in China.

You are very familiar with the strengths and needs of the Chinese Health Care system. Can you give us an idea of the assets and challenges of the practice of NM in China?

China is a big country with over 1.3 billion population. Dealing with health and medical care problems is really a huge project. Chinese government has worked out policies and provided financial supports to guarantee that every citizen, no matter urban or country inhabitants, be covered by medical insurance. However, due to the huge population, the level of current medical insurance service is basic. SPECT and SPECT/CT studies, which are reimbursed by medical insurance, play a very important role in diagnosis and prognosis of various diseases, especially on tumor and cardiac diseases, evaluation of therapeutic effects, and guiding individual strategy of therapy. In addition, both hyperthyroidism and thyroid cancer treated by ^{131}I therapy are also reimbursed by medical insurance. However, in most provinces and cities, PET/CT studies haven't been reimbursed by medical insurances. Besides insurance problems, there are several other difficult problems and challenges we have to face. For example, ^{99}Mo-^{99m}Tc generators are, at times, in short supply. Furthermore, some important imaging agents, such as ^{123}I-MIBG, cannot be regularly obtained in China. Besides that, the shortage of professionals is one of the big challenges to the development of nuclear medicine in China in the future.

China is the fastest growing nuclear medicine community in the world. How can the world nuclear medicine community contribute to the success of your and the Chinese Society of Nuclear Medicine endeavors?

CSNM always devotes itself to communicating with the world nuclear medicine community since it was established. During the recent years, many staff members attended SNMMI and EANM to present their works and the progresses of nuclear medicine in China. Many young students studied aboard and came back to China. Meanwhile, many experts worldwide also have made great contributions to the development of nuclear medicine in China via multiple ways, for example, by introducing their latest developments in nuclear medicine in China and by collaborating with Chinese nuclear medicine centers. Finally, we hope that the world nuclear medicine community could offer more learning opportunities for Chinese professionals of nuclear medicine and help CSNM to develop and promote the development of nuclear medicine technology for medical services, especially in oncology, cardiology and neurology in China.

You have had the opportunity to read the first issue of the NM magazine Pangea-ePatient. What do you think of the magazine and what would your suggestions be to improve it?

The Pangea-ePatient magazine is not confined to the traditional approach of nuclear medicine journals. It explores a new educational and practical tool adapted to the current educational needs. It is a rewarding magazine which provides people from different disciplines rich information. After reading the first issue of the Nuclear Medicine magazine Pangea-ePatient, I like this journal very much. In the first issue, many different perspectives are presented, including code of operation, education and training, scientific research progress and the development of nuclear medicine. Additionally, this magazine uses a variety of languages, which is really unique! However, considering the journal's international purpose, we believe English may be the best choice as it is the official language. Thank you very much.

Michael Rossi
President, Jubilant Jubilant DraxImage
Montreal, Canada

Interview with: Mike Rossi

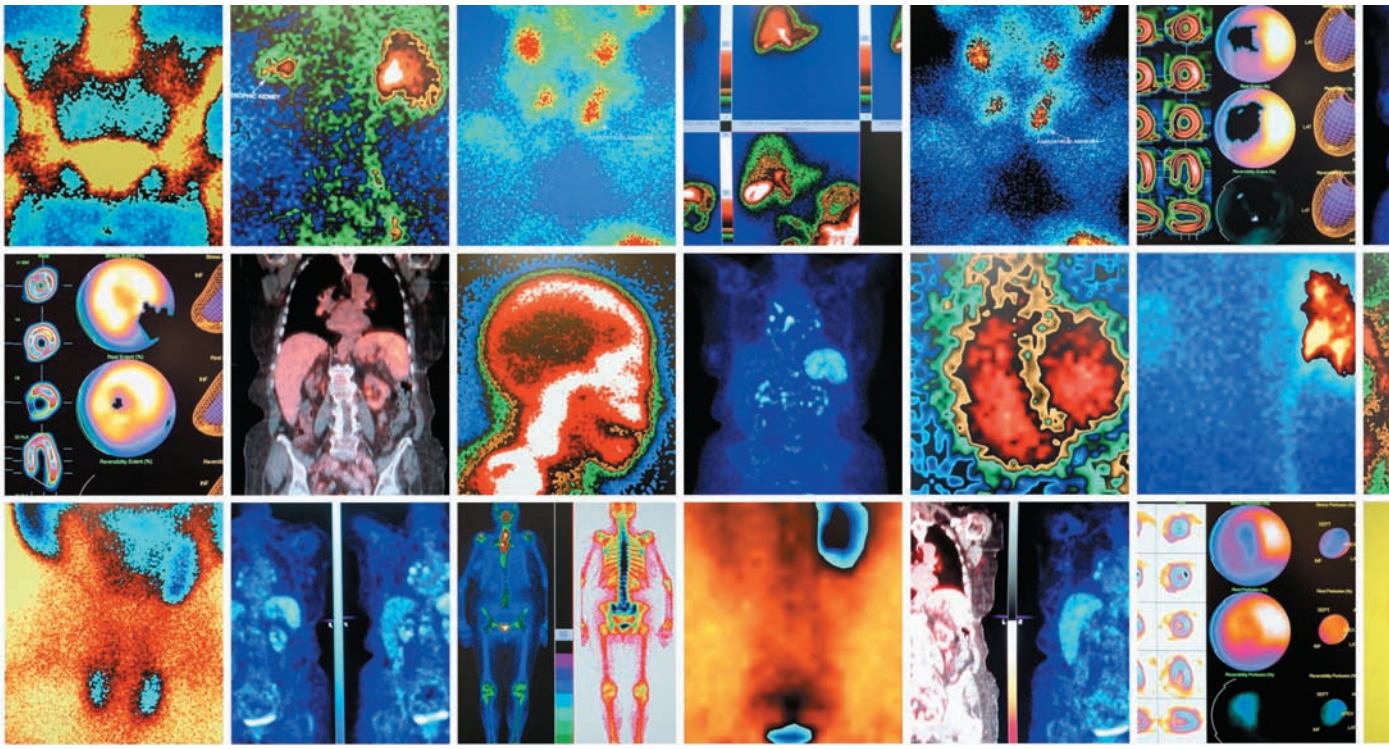
Over the past decades, as a nuclear pharmacist, you have witnessed many changes in the world of radiopharmacy in North America and the rest of the globe. What are the landmarks changes that you have seen over the past 30 years?

The field of nuclear medicine has seen several significant changes over the past few decades. The evolution of SPECT and PET technologies brought a resurgence in the number of patients being imaged in nuclear medicine departments across the globe. From 1995-2005, we saw almost a doubling of the number of procedures being performed. To support this growth and to help doctors focus more on patients rather than compounding radiopharmaceuticals, the radiopharmacy unit dose business blossomed and became the norm in many areas of the world by the mid 90's.

North America continues to lead in the number of radiopharmacies and I have seen a dramatic improvement in the quality and services radiopharmacies provide to their customers. Spending many years early in my career as a radiopharmacist, I understand the significant contribution these facilities can have on their customers and their local communities. They create economic, time, and regulatory efficiencies for physicians, so that they can focus on providing their patients the best care possible. I believe these facilities will be instrumental to the longevity of this modality.

With the end of isotope production at the Canadian Reactor at Chalk River, the nuclear medicine community had to find new sources for medical isotopes. How did a company like Jubilant DraxImage adapt to the new world map of medical isotope production?

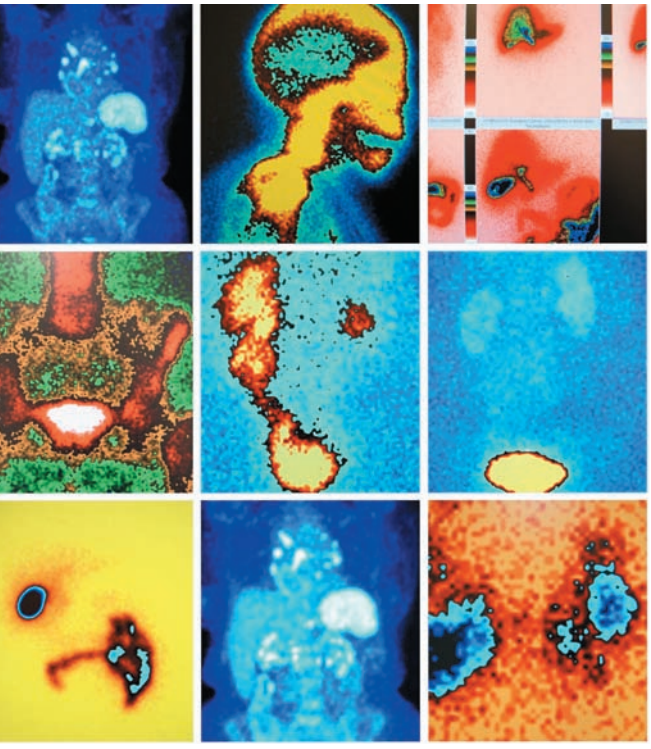
Jubilant DraxImage (JDI) understands the need to adapt and is proud of our long and deep relationships with multiple global suppliers of medical isotopes. The availability of supply supports the foundation of nuclear medicine imaging and its sustainability for the future. This sustainability, is dependent upon the constant and uninterrupted supply of quality isotopes, which allows for new and innovative



drugs to be developed. We continue to maintain strong partnerships with multiple reactor based producers of isotopes world-wide. We also know that the changes in the global production map is due in small part to the necessary shift from the use of High Enriched Uranium (HEU), that has potential negative uses outside of medicine, to exclusively non-High Enriched Uranium (non-HEU), which does not.

We also have a strong supply chain team made up of dedicated professionals that proactively and continuously evaluate the shifting landscape of isotope production on a regular basis. We must stay engaged so that we can plan for these shifts, rather than react to them.

These combined factors have proven to be invaluable to us. In fact, just recently, we received approval from the US Food and Drug Administration (FDA) for an additional supplier of an Iodine Isotope (I-131), prior to an unplanned production stoppage by another supplier. Without this additional supply, patients around the world would go untreated for an indefinite period of time until normal supply levels of I-131 returned. This is just another demonstration of JDI's long term commitment to the nuclear medicine community. Our goal is to ensure both consistent supply of these important diagnostic and therapeutic agents to health care professionals so they can provide their patients with the personalized care they deserve, as well as the sustainability of Nuclear Medicine, so future patients can continue to receive the many, and often unique benefits of these products.



Personalized medicine, molecular imaging and treatment targeting are becoming an integral part of the practice of medicine. How do they affect the vision and strategies of DraxImage?

Personalized medicine is the driving factor for what we do and has long been the goal of molecular imaging, the Nuclear Medicine community and our business. The reality is that nuclear medicine is the only modality that provides a true functional or pathophysiological imaging assessment, as compared to other imaging techniques that primarily show only the anatomy of disease or disease process. It provides doctors specialized tools to meet the unique needs of an individual patient. This is directly in line with JDI's vision of improving lives through nuclear medicine. In fact, over the past few years we have taken great and meaningful strides towards this goal by investing in radiopharmaceuticals and partnering with therapeutic companies.

The mission of our R&D team is to continually work towards developing new "theragnostic agents" that will prove to be invaluable to physicians; allowing them to accurately diagnose patients earlier, provide treatment, and to monitor the progression of disease and the patient's response to these personalized therapies. This approach will lead to better patient care, outcomes, and quality of life, which is our ultimate goal.

Jubilant DraxImage has been a great supporter of NM educational initiatives. In your opinion, what role do you see the Pangea-ePatient magazine play for the practice of nuclear medicine?

As you note, JDI is a strong supporter of education and quality and the benefits they provide to patients, diagnostic and therapeutic procedure performance and to Nuclear Medicine's sustainability. To this end, we fully support the Pangea-ePatient magazine because it provides patient education that helps answer their questions and provides further clarity about their procedures. In today's world, easy access to information, primarily driven by social media, has created a society with a more educated patient. We support this and other ongoing patient education efforts because we believe that knowledge gives patients the power to make more informed decisions about their own, or a loved one's, medical care. Importantly, this information must be accurate and understandable. Pangea-ePatient magazine accomplishes this and focuses on patients in Nuclear Medicine that fills a very important educational void. ■

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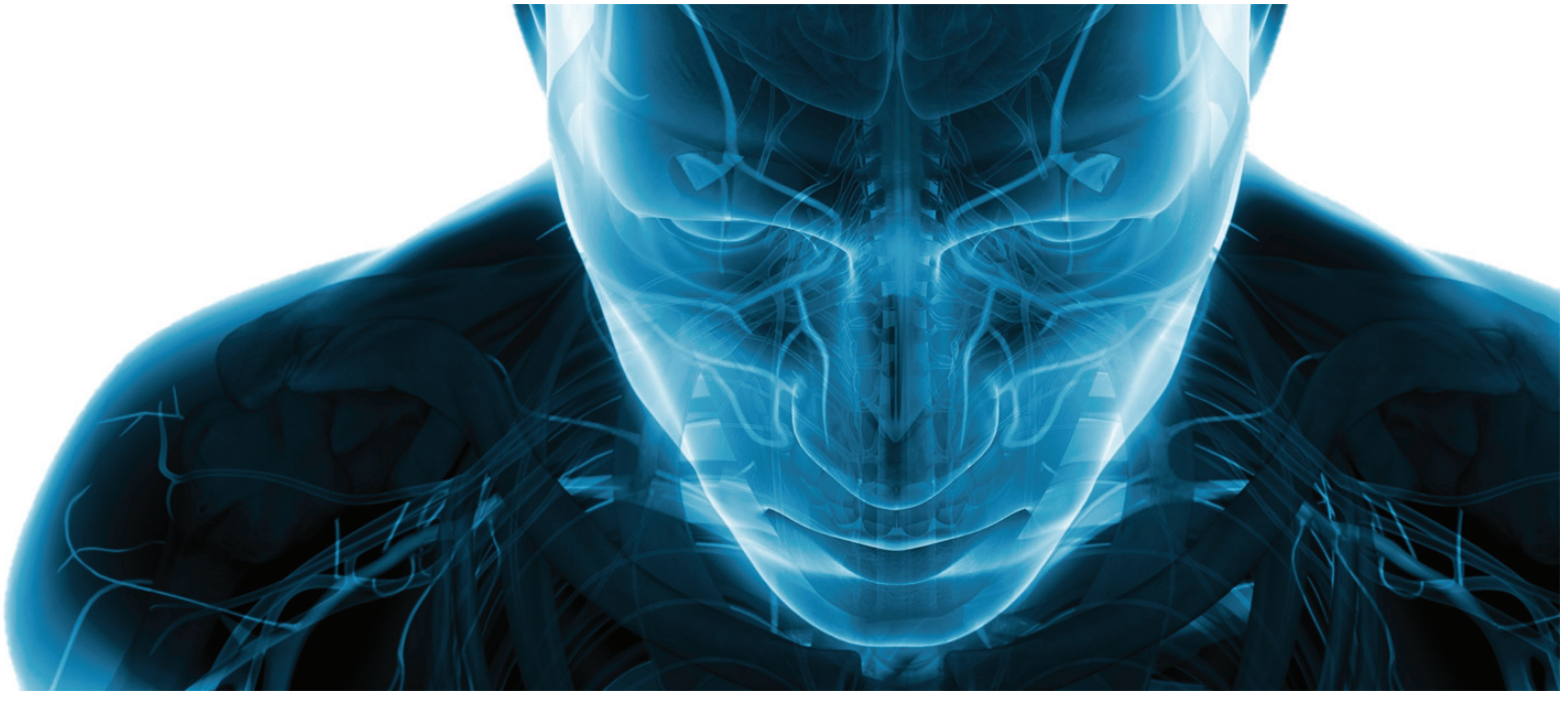

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Mohamad B. Haidar M.D.
Vice-President, Arab Society of Nuclear Medicine (ARSNM)
Director, Nuclear Medicine Division and Cyclotron Facility
American University of Beirut Medical Center, Beirut, Lebanon

The role of Nuclear Medicine in the Diagnosis of Brain Diseases

The article, written by Dr. Mohamad Haidar and Dr. Akram Al-Ibraheem, is available in Arabic on the magazine web site at www.nmpangea.com

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Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

For more information please consult the product monograph at http://www3.gehealthcare.com/~/media/Documents/MarketoPDFsnogating/ProductMonographCanadaControlNo201481December72017.

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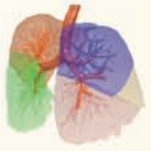
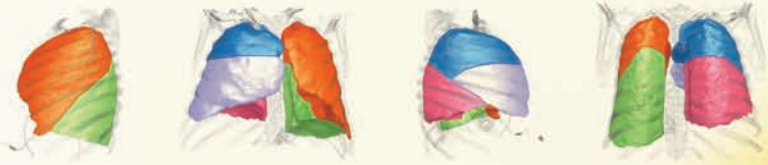


	Volumes [%]		Perfusion [%]		Ventilation [%]	
	Right	*Left*	*Right*	*Left*	*Right*	*Left*
Upper	24.1	19.1	29	16.2	31.1	9.48
Middle	17.4	N/A	11.5	N/A	23.4	N/A
Lower	15.9	23.4	17.6	25.7	16.1	20
Total	**57.4**	**42.6**	**58.1**	**41.9**	**70.6**	**29.4**



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