Special Contribution

THE NEW DIRECTION OF NUCLEAR MEDICINE

David Greyson, MD

Department of Medical Imaging and St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada

ABSTRACT

The role of the nuclear medicine has changed, from the early days when it was the only alternative to x-rays, to the present, when nuclear images are interpreted in light of specific metabolic processes, not anatomy. The development of specific receptor targeting radiopharmaceuticals, markers of viability using PET or SPECT, analogues of neurotransmitters etc., have placed the nuclear medicine physician into the realm of an *in vivo* biochemist or pharmacologist, or an applied physiologist. The current role of nuclear imaging is not merely to detect an abnormality, but to characterize the pathophysiology, risk stratify, direct therapy, and offer prognosis. As we recognize that the information obtained from a scintigram is occurring below the cellular level, we are entering the age of "Molecular Nuclear Medicine".
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Key words: mapping pathophysiology; in vivo pharmacologist; molecular nuclear medicine

INTRODUCTION

From the time it became clinically useful in the mid 1960's, Nuclear Medicine was considered to be the alternate to x-rays as an imaging modality. That role was emphasized as the gamma camera was improved, and Technetium-labeled radiopharmaceuticals became more versatile. This was particularly true of nuclear medicine's ability to image soft tissue organs, such as liver, brain, kidneys, etc. However, with the subsequent developments of ultrasound, CT, and MRI, with improved soft tissue resolution, the "death of Nuclear Medicine" was predicted as each new technique was introduced.

Nuclear Medicine remains a strong, and increasingly useful modality, as it is recognized as the only modality which reflects *in vivo* biological processes, and is less used as a substitute for structural imaging. Unique among imaging modalities, nuclear medicine is based on the metabolic interactions of the tissues with administered radiopharmaceuticals. This is an area of rapid growth, with new classes of agents being developed to image more specific diseases, and various physiological pathways. The following presentation outlines only a few of the newer concepts of nuclear imaging.

Molecular nuclear medicine

Nuclear Medicine images have much poorer spatial resolution than other current Diagnostic Imaging modalities, due to limitations imposed by count rate and detector technology. However, as has been pointed out by Wagner, and others (1-3), that by analyzing the radiopharmaceutical distribution, diseases and physiological processes can be classified by their biochemical activities. Although structural resolution is

poor, the distribution of the radiopharmaceutical is at the molecular level within the cell. Thus, the concept of "Molecular Nuclear Medicine" is being adopted. Wagner (3) suggests that in the future, diseases will be viewed as biochemical processes, rather than clinical manifestations of these processes.

The correlation of Nuclear Medicine, with Diagnostic Imaging is thus very relevant, because the information is so different, yet complimentary. As with the prediction of the weather, where the details of atmospheric changes must be superimposed on an accurate geographical map, the combination of structural and physiological imaging produces great synergy for diagnosis.

The new role of Nuclear Medicine has transcended organ imaging, but is now used in the prediction of therapeutic response, risk stratification, biochemical classification of diseases, etc.

Antibody and receptor imaging

Early radiopharmaceuticals used crude properties of localization for organ imaging, such as phagocytosis, blood pool volumes, passive diffusion, etc. Currently, some radiopharmaceuticals are being synthesized to take advantage of specific receptor sites within the cell, or on cell membranes.

The imaging of specific benign or malignant tissues with monoclonal antibodies still holds great promise. Applications in the detection of colorectal, ovarian, and other cancers, and thrombosis, remain important research directions (4). However, the complex technology required in the *in vivo* production of antibodies in laboratory animals, followed by the cloning and tissue culture processes are very complex and expensive. The antibody itself is generally a large molecule, with poor specificity and slow localization. There is also a significant risk of inducing human antimouse antibodies, (HAMA) in the patient (5).

The active site of interaction of the monoclonal antibody is at a peptide chain at the end of an antibody, which locks into a specific locus on the target. After analysis of the peptide chains on the antibody, it is now possible to synthesize the active peptide foci and bypass the antibody production step.

As the nature of these peptide bonds become better elucidated, we can expect a wide variety of these agents, hopefully with higher specificity, and rapid localization, and improved target to background discrimination (6,7).

Somatostatin receptor imaging

The most widely known current application of labeled peptide imaging is that of the somatostatin analogue, octreotide (8). Somatostatin is a neuropeptide, produced produced in the hypothalamus. It has a wide variety of regulatory, or inhibiting activities, acting on the release of growth hormones, and on other endocrine cells, inhibiting cell growth, and neuronal activity. Pharmacologically, it has been used in the treatment of tumors associated with neuroendocrine hyperfunction, such as carcinoids, gastronomas, and insulinomas.

Somatostatin receptors have been identified on a variety of tumors, such as neuroblastomas, medullary carcinoma, lymphomas (9), thymomas, and brain tumors. Labeled somatostatin analogues are also localized in these receptor sites (10). The synthesis of eight amino acid (octreotide), or five amino acid (pentreotide) (11), labeled with either radioiodine or indium has produced an important class of radiopharmaceuticals to detect and characterize primary and secondary neoplasms (Figs. 1A and 1B).

The localization, however, requires the presence of somatostatin receptors. Thus, a positive scan may demonstrate the distribution of the abnormalities, and also predicts the potential for the therapeutic use of somatostatin.

Somatostatin receptors have also been found on activated lymphocytes, and on certain lymphoma cells. Lipp (9) demonstrated an overall sensitivity of 70%, with 88% detection in head and neck lesions, but only 13% within the abdomen and pelvis. The varied pattern of the sensitivity of deposition of this radiopharmaceutical suggests that it may be less useful for specific detection of lymphomas, but that it may be able to characterize the lesion based on that physiological property. This could lead to new methods of classifying tumors.

Lee (12) noted poor uptake in malignant gliomas, while low grade astrocyomas retained somatostatin receptor sites. Not only does somatostatin suppress the functional activity of its target cells, but because of its inhibition of growth hormone, it may also have some inhibitory effects on tumor growth, and improved survival (11). Thus, the presence, or absence of somatostatin receptors on some tumors, may have a significant impact on patient management.

Viability markers

Traditional Nuclear Medicine techniques diagnosed necrosis by the absence of blood flow. This was the approach used in detecting avascular necrosis of bone, splenic infarcts, etc. However, current experience in the evaluation of cardiac ischemic disease with both PET and SPECT tracers has deepened our understanding of the relationship of blood flow and viability. (See Supplement to the Journal of Nuclear Medicine 1994, Vol. 35, No. 4, for a symposium on this topic).

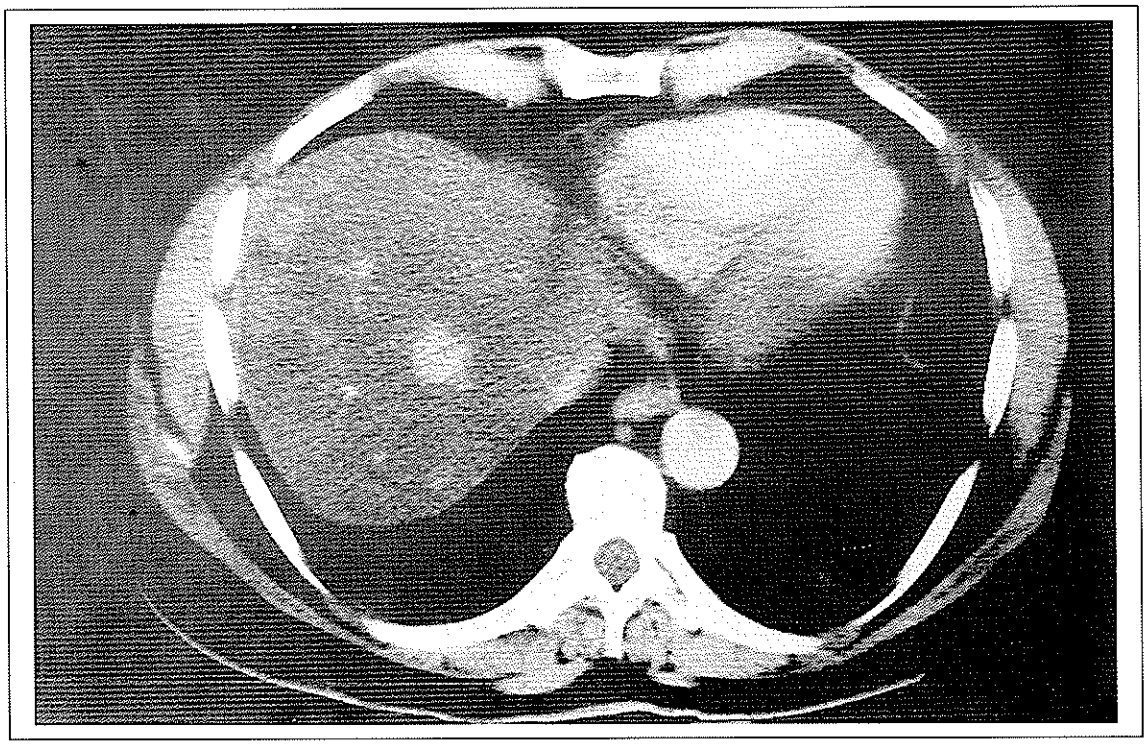

Fig. 1A. A 42-year-old female presenting with severe diarrhea. CT of the abdomen shows several high density nodules in the liver, consistant with metastases.

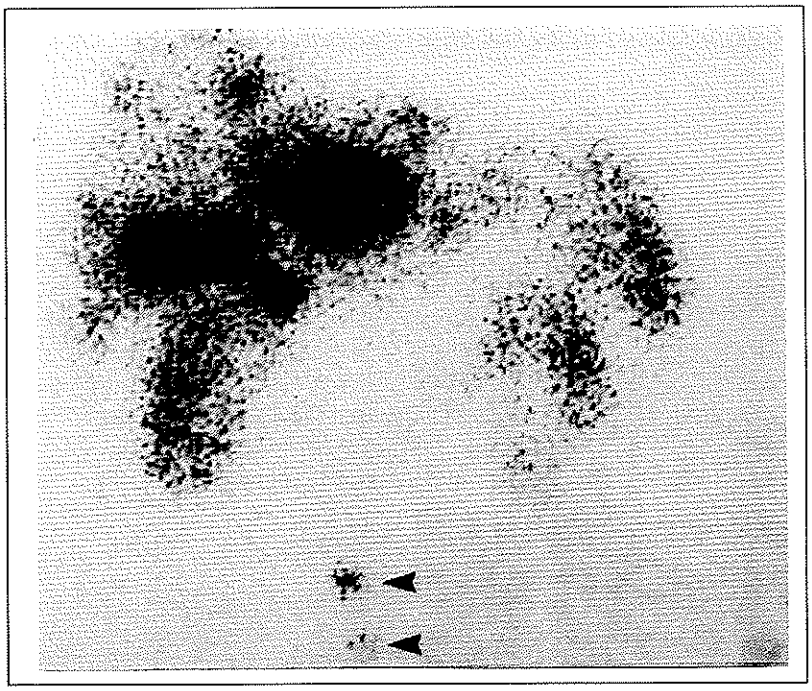

Fig. 1B. Indium-111m-octreotide scan of the abdomen. There are multiple foci of intense uptake in the liver,corresponding to the metastases. In addition, two lesions in the mid abdomen (arrows) corrspond with intraluminal nodules in the small bowel seen on a barium study. Metastatic carcinoid tumor was diagnosed. The positive uptake in the lesions predicted favorable response to somatostatin therapy for symptoms.

Thallium-201, or Technetium-99m Sestamibi scans of myocardial perfusion may demonstrate areas of reduced cardiac blood flow, but both of these agents underestimate viability. In locations where motion studies show decreased contractility, and perfusion is abnormal, the usual supposition is that there is fixed scarring of the myocardium due to necrosis. This has been demonstrated to be incorrect in many patients.

Fluorine-18-desoxyglucose (FDG), is a positron labeled tracer of the pathways of glucose metabolism. Even in severely suppressed living tissues, some glucose metabolism must be present. The use of FDG PET imaging has confirmed the presence of preserved viability in localized hypoperfused and hypokinetic myocardium. Acute ischemia may result in a "stunned" myocardium, while chronic coronary insufficiency may produce a "hibernating" myocardium, but these areas are not dead tissue. The combination of the myocardial perfusion image, and the FDG metabolic image may show a discordant pattern of unmatched defects, indicating that while there is a functional disturbance, there is still viability within the myocardium. Matched perfusion abnormalities and glucose metabolic defects are consistent with necrosis.

The role of viability imaging is to demonstrate the potentially salvageable component of the damaged myocardium. This assists in evaluating prognosis, and risk stratification of patients selected for interventional therapy.

The need for a cyclotron, and dedicated PET camera has restricted the use of this technology to research centres. However, recently, gamma cameras are being modified to permit imaging of the 511-keV photon derived from positron annihilation. Imaging techniques use standard emission tomography with very high energy collimators, or use coincidence counting, in a two headed gamma camera, with the heads positioned at 180 degrees in apposition. Clinical results are comparable to those obtained with a dedicated PET camera but at much lower cost.

Tumor imaging

Gallium-67 is a widely used radiophamaceutical, but it is a relatively non-specific tumor marker with a variety of complex mechanisms which result in its localization. These include increased vascularity, increased capillary permeability, the presence of iron binding proteins within the tumor, and a high concentration of endoplasmic reticulum (gallium-binding granules) in the cytosol. Inflammatory, and neoplastic lesions cannot be differentiated.

The detection of tumors is also possible using FDG imaging (with either a PET or SPECT 511-keV camera). This pharmaceutical demonstrates the presence of increased glucose metabolism within the lesion. It can differentiate neoplasms from other, non-neoplastic tissue, which may have similar imaging appearances on CT or MRI. Thus, a lung carcinoma may be differentiated from adjacent pulmonary fibrosis or benign enlarged lymph nodes, and the recurrence of a brain tumor may be differentiated from areas of post-operative gliosis, or radiation necrosis of the brain.

Technetium-99m-Sestamibi, originally developed as a myocardial perfusion agent has also been shown to have valuable tumor-seeking properties. The localization of Sestamibi requires sufficient blood flow, but the intracellular binding is dependent on the mitochondrial wall membrane potential (13). Thus, it can define areas of increased cellular metabolism, and has a similar use to FDG.

Sestamibi imaging of brain tumor (14), thyroid (15), lymphoma (16), and other cancers, has been reported (Figs. 2,3A, and 3B).

Recently, reports of the role of Sestamibi in breast tumor imaging have appeared (17, 18). The authors report sensitivity and specificity in excess of 90%. Conventional mammography, widely used for the detection of breast carcinoma, relies on very specific radiographic patterns to screen patients for biopsy or surgery. However, in the presence of dense breasts, or multiple benign calcifications, there is much reduced specificity of the mammogram. There is a high frequency of benign breast biopsies, indicating the lack of radiographic specificity. The use of Sestamibi helps direct the site of biopsy. There is also a high sensitivity and specificity for the detection of axillary lymph nodes, which is important in the staging of patients for therapeutic protocols.

Other radiotracers, such as somatostatin receptors, and MIBG markers are also used for tumor scanning. These define specific metabolic pathways within the tumor cells. There is some overlap in the spectrum of tumors which may concentrate either MIBG or somatostatin, and in a patient with primary or metastatic tumors, comparing images with both of these tracers may show significant differences. Any given focus of the tumor may show activity in either, or neither, or both radiopharmaceuticals. The significance of this discordance is not yet clear but research may lead to a better understanding of the microphysiology of these tumors, or a new pathological classification based on this property. However, generally, tumors with avid uptake of octreotide indicate the presence of somatostatin receptors which indicates a high likelihood of therapeutic response

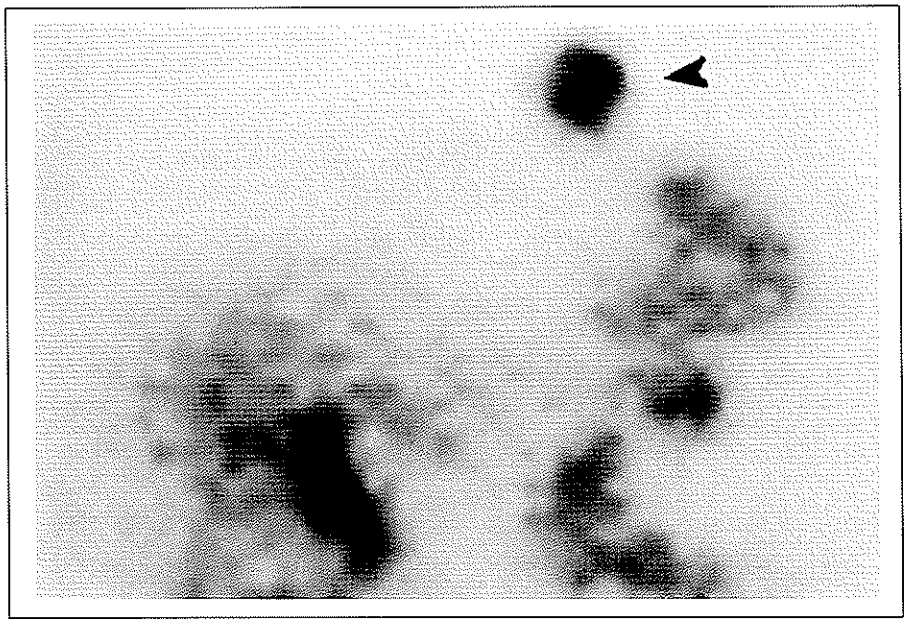

Fig. 2. planar Te-99m-MIBI view of the chest. There is uptake in a mediastinal tumor, thought to be a thymoma, found incidentally during acquisition of a myocardial perfusion scan.

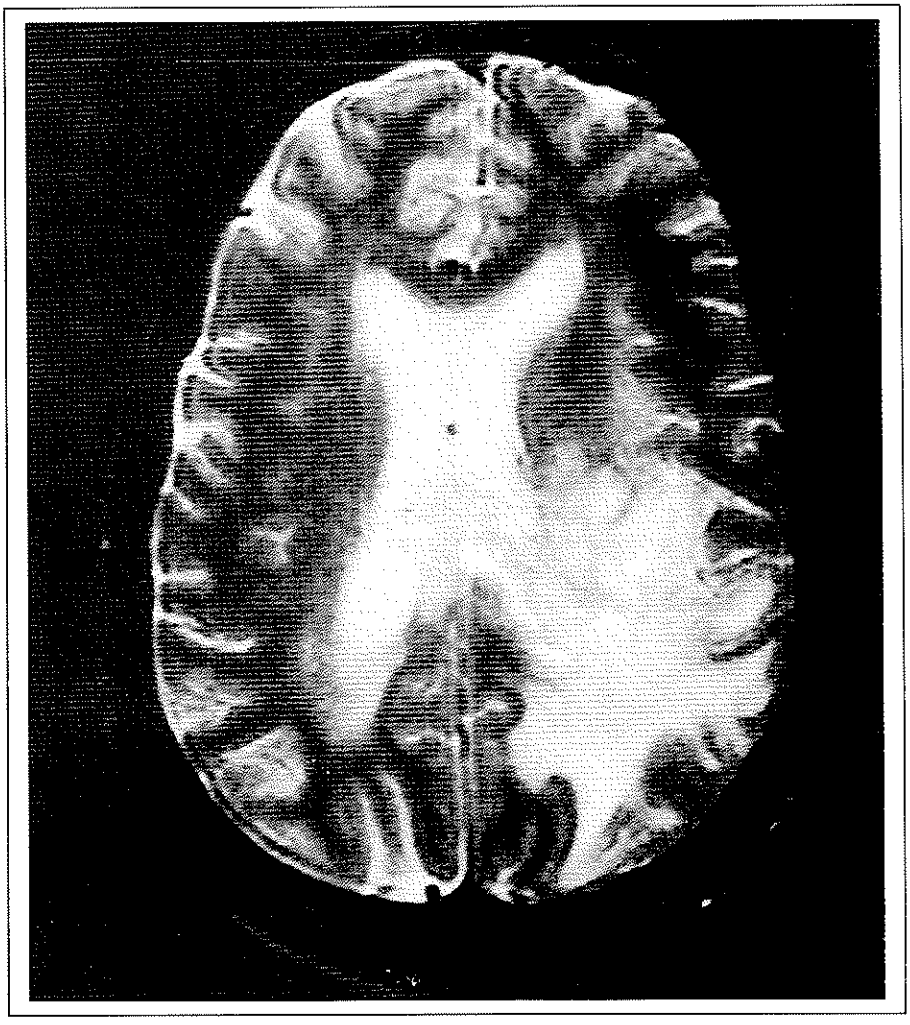

Fig. 3A. MRI image of the brain in a patient with previous resection of a malignant glioma, and radiation therapy. There is a large lesion with hetrogeneous signal response in the left posterior parietal region. The appearance could represent post-irradiation necrosis, benign gliosis, or tumor recurrence.

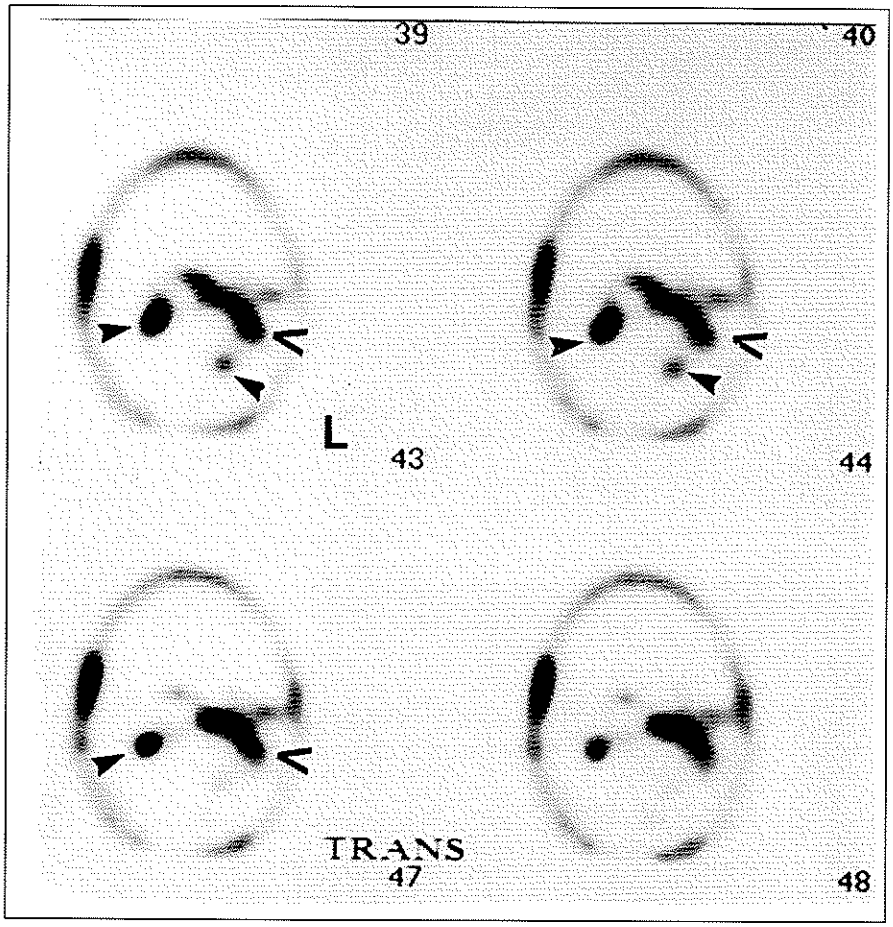

Fig. 3B. SPECT Tc-99m MIBI images of the head. There is normal uptake in the choroid plexus (solid arrows). The left choroid is displaced posteriorly. There is abnormal uptake (open arrow) in the left parietal area,corresponding to the anterior part of the large MRI lesion. This was tumor recurrence, while the rest of the lesion was benign.

to somatostatin medication (19). Future work with estrogen receptor imaging may be predictive of the potential response of tumors to tamoxifen.

Prediction of multidrug resistance (MDR)

Some patients with cancer show very poor response to traditional chemotherapeutic agents. This phenomenon is associated with the expression of P-glycoprotein on the cell membrane which has a role in actively excluding some of these chemotherapeutic drugs from the cell. It has been noted, that the same mechanism increases the efflux of Sestamibi from those tissues. It is now felt that the absence of localization of Sestamibi in a tumor may correlate with multidrug resistance. This has significant implications for therapeutic decisions, as it may predict response to chemotherapy, prior to the treatment (20,21).

MIBG for cardiology applications

Iodine-123 or Iodine-131 labeled metaiodobenzyl-guanidine (MIBG) is a marker of the sympathetic nervous system. There is intracellular storage of this material, paralleling the deposition of norepinephrine in chromaffin granules. This pharmaceutical has been used in the detection of tumors of sympatho-adrenal origin, such as pheochromo-cytoma, paraganglioma, neuro-blastoma, carcinoid and medullary thyroid carcinomas (22,23).

There is, however, some deposition of this agent within normal tissues including transient localization in the myocardium, within the first few hours after injection. MIBG localizes within the sympathetic pathways of the myocardium. Recently, it has been used to detect abnormalities in cardiomyopathies, such as diabetes, and doxorubicin cardiomyopathy, where atrophic nerve fibres have been demonstrated histologically (24,25). This provides another technique for detecting and characterizing the pathology leading to cardiac dysfunction.

CONCLUSIONS

Nuclear Medicine has always been an answer, in search of a question. With more refined radiopharma-

ceuticals, and better understanding of the physiological mechanisms of deposition, our questions are becoming more sophisticated and specific, and hopefully more meaningful to patient care.

We no longer compete with the high spatial resolution of structural imaging technologies. Instead, Nuclear Medicine physicians should consider the mechanisms of localization, and realize that we are mapping physiology or pathophysiology.

It is no longer sufficient to detect a tumor. We can now define many aspects of its biochemical nature, and its metabolic pathways, and predict its response to treatment. These markers may result in an altered classification of disease.

It is no longer sufficient to diagnose coronary artery disease, but we are able to define prognosis, and predict the potential results of surgical intervention.

The new role for the Nuclear Medicine Physician is that of an in vivo pharmacologist and biochemist. This defines a new direction, and a brighter future for the newer, clearer, Nuclear Medicine.

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