Positron Emission Tomography

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Basic Sciences

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Preface

In 2003 we published *Positron Emission Tomography: Basic Science and Clinical Practice*. The aim of that book was to address what we perceived of as a lack, at the time, of a comprehensive contemporary reference work on the rapidly expanding area of positron emission imaging. The scope was intentionally wide. The original proposal for a 350 page book turned into a nearly 900 page volume.

This book, *Positron Emission Tomography: Basic Sciences*, is a selected and updated version of the non-clinical chapters from the original book. In addition, a number of new chapters have been added which address the role of PET today for the scientist currently working in or entering this rapidly expanding area. The audience that this is intended for is the scientist, engineer, medical graduate or student who wants to learn more about the science of PET. Many of the chapters have been updated from the original to reflect how rapidly the technology underpinning PET is changing.

The following diagram encapsulates much of what is required in understanding the science of PET. It is taken from an introduction by Professor Terry Jones to a book of the proceedings from a PET neuroscience conference in the mid-1990s. It is the intention of this book to deal with the majority of these topics and to produce a comprehensive "science of PET" textbook which is more focussed and manageable than the original volume. We hope this book will be of use to you.

Finally, we are sad to report that the principal editor of the original work, Peter E Valk, *MB*, *BS*, *FRACP*, passed away in December 2003. Peter was a great friend and outstanding advocate for, and practitioner of, nuclear medicine and PET. He will be greatly missed by his many colleagues and friends everywhere. We are indeed fortunate that Peter left us with a truly wonderful book on PET to preserve his memory and not let us forget the debt that we owe him for the leading role he played in bringing PET into clinical patient care.

Dale L Bailey
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Sydney, Knoxville, London
March 2004

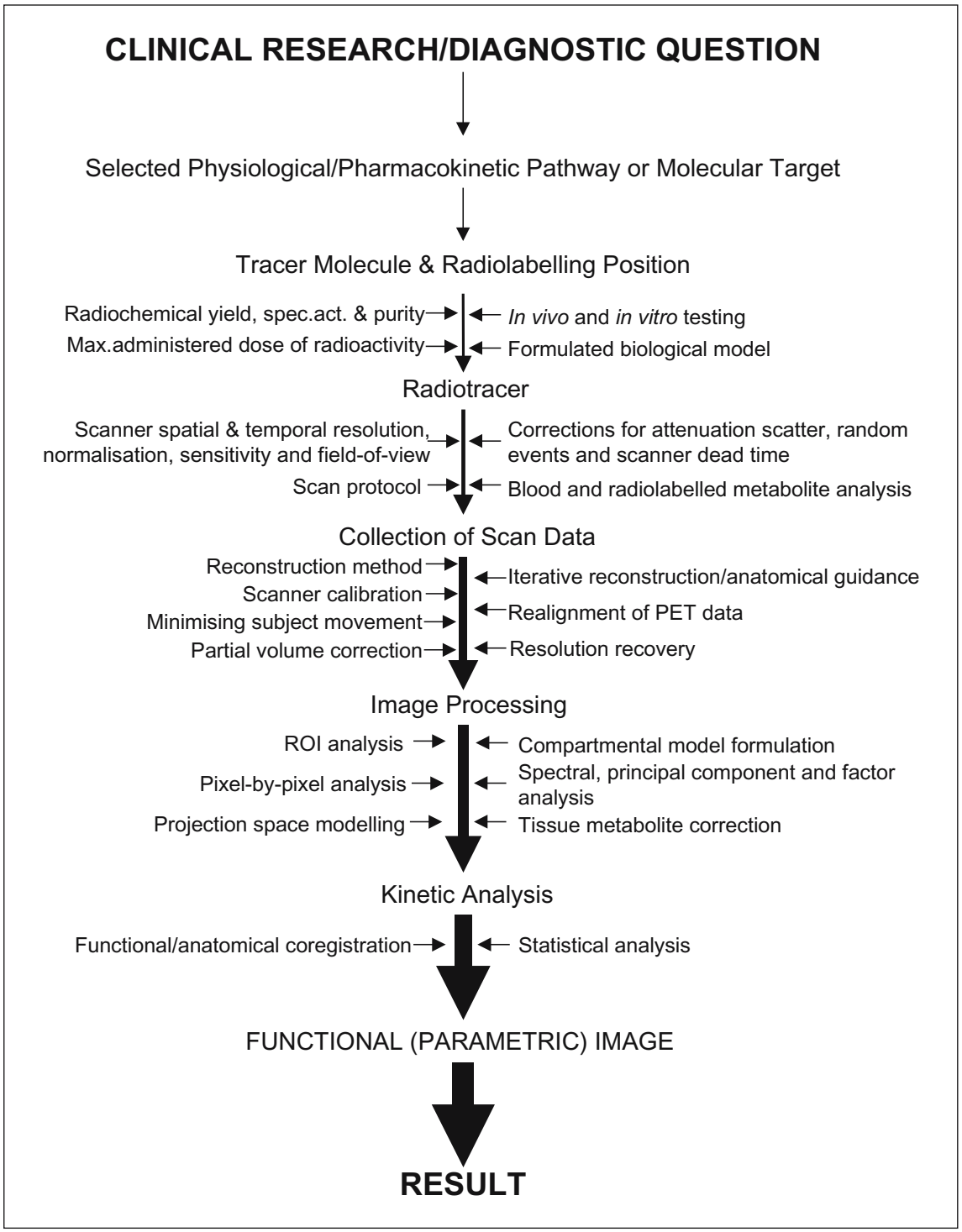

Figure 1. Jones' view of the science of PET (adapted from Myers R. Cunningham VJ, Bailey DL, Jones T (Eds): *Quantification of Brain Function with PET*. Academic Press; 1996 and used with Professor Jones' permission).

Contents

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1 Positron Emission Tomography in Clinical Medicine

Michael N Maisey

Introduction

Positron emission tomography (PET) imaging is set to change the whole impact and role of Nuclear Medicine, not because it does everything better than conventional single photon imaging (planar and single photon emission computed tomography (SPECT)), but because it also has the impact and public relations of the fastest growing diagnostic speciality. PET is a powerful metabolic imaging technique utilising possibly the best radiopharmaceutical we have ever used [^{18}F]-fluorodeoxyglucose (FDG). However, in addition, it yields excellent quality images, the importance of which can be appreciated by non-nuclear medicine clinicians, and has an enormous clinical impact, as demonstrated in many well-conducted studies. Any oncologist exposed to a good PET imaging service very quickly appreciates its value. Sitting in on routine clinical PET reporting sessions, it is easy to appreciate how patient after patient is having their management changed in a very significant way as a direct result of the new information provided by the PET scan.

There is now an impressive body of data evaluating the impact of PET on patient management. These studies are showing that PET results alter management in a significant way in more than 25% of patients, with some as high as 40%[1]. Examples include changing decisions on surgical treatment for non-small cell lung cancer (both avoiding inappropriate surgery and enabling potentially curative resection), the staging and treatment of lymphoma, decisions on surgical resections for metastatic colo-rectal cancer, referral for revascularisation of high-risk coronary artery disease (CAD) patients and many others. This is a level of impact on patient care for common and life-threatening diseases not previously achieved by Nuclear Medicine. Nuclear Medicine has always improved patient care, but usually marginally, such that it has sometimes been difficult to argue that good medicine could not be practised without it. This has often resulted in limitations on the manpower and other resources being put into Nuclear Medicine, particularly in health care systems functioning at the lower end of gross national product (GNP) percentage investment, such as the National Health Service (NHS) in the United Kingdom. This is not true of PET. It is no longer possible to practice the highest standard of clinical oncology without access to PET, and it is clear that without it many patients are needlessly undergoing major surgical procedures and many are being denied potentially curative treatments. If PET and X-ray computed tomography (CT) were to be introduced simultaneously now for oncology staging, follow-up, assessment of tumour recurrence, evaluation of treatment response, *etc*, there would be no competition with PET proving vastly superior in these areas of cancer patient management.

We therefore have in clinical PET a new imaging tool as part of Nuclear Medicine which has brought the speciality to the very heart of patient management, especially for Oncology, but also in Cardiology and Neuropsychiatry. Nuclear Medicine has always been excited by the potential for new ligands for clinical application and the study of patho-physiology. Although for many reasons the potential has not been fully delivered, it may be that the future role of PET ligands will be huge, especially as we are on the brink of molecular and genetic imaging. Furthermore, for PET to be the

future of Nuclear Medicine we do not need to argue on the grounds of the potential, as, with FDG, we have the most effective and powerful radiopharmaceutical of all time. Nuclear Medicine has never had a single tracer which could study brain metabolism, cardiac function, image sites of infection, and detect cancer as FDG does in thousands of scans world-wide every day.

Technical developments will also drive the widespread introduction of PET as the main developing area of Nuclear Medicine. PET scanners are becoming significantly more sensitive leading to considerably faster patient throughput, as long scanning times were one of the weaknesses of early scanners. "Fusion imaging", always a promising "new" methodology, has been kick-started by the combined PET/CT concept (see chapters 8 and 9). However, the greatest benefits of fusion imaging may eventually come from software, rather than hardware, fusion because of the flexibility of fusing multiple imaging modalities with PET (*e.g.*, magnetic resonance imaging (MRI)) as well as image fusion of sequential PET images over time, which will be of increasing importance for PET-based molecular and metabolic imaging when used for following the response to treatment. The spatial resolution of PET images is also improving, so that metabolic images with millimetre resolution are increasingly probable. The power derived from quantification will be revealed as measurement of early tumour responses becomes routine practice. Many of these benefits are because of the investment of time and money that industry is putting into PET as it is perceived as a major area of expansion.

With increased patient throughput and a greater number of PET scanners and imaging resources, there are opportunities for PET methodologies to be used for studies such as bone scans (with [^{18}F]-F^{-} or FDG, or even a combination of the two), all cardiac perfusion and myocardial viability studies, and many other current SPECT-based studies (*e.g.* imaging neuroendocrine tumours using [^{111}In]-octreotide or [^{131}I]-mIBG) could be performed by PET. A lot will depend on the inventiveness and will of the cyclotron operators and radiochemists who will be responding to the clinical agenda.

Current Clinical Applications of PET

Clinical PET imaging, almost exclusively with FDG at present, is being used in three important areas of clinical diagnosis and management:

- Cancer diagnosis and management
- Cardiology and cardiac surgery
- Neurology and psychiatry.

Each of these areas will be examined in more detail.

Cancer Diagnosis and Management

Although FDG is by far the most important radiopharmaceutical at present others such as ^{11}C-labelled methionine and choline and fluorine labelled DNA proliferation markers such as fluoro-L-tyrosine (FLT) will have an increasing role in the years ahead. The applications can be classified according to the generic use for which the PET scan is applied, that is detection, staging tumour response, *etc* or by tumour types. Both are important to understand although the tumour type approach will be the method chosen for agencies responsible for agreeing reimbursements.

- *Diagnosis of malignancy*: examples will include differentiating malignant from benign pulmonary nodules, and differentiating brain scarring after treatment (surgery, chemotherapy and radiation therapy) from tumour recurrence.
- *Grading Malignancy*: as the uptake of FDG and other metabolic tracers is related to the degree of malignancy (the principle established by Warburg in the early part of the 20th century[2]) the PET scan can be used to grade tumours and therefore indirectly provide information on prognosis (the so-called "metabolic biopsy").
- *Staging disease*: staging is documenting how widespread the cancer is in the patient. The PET scan has been show to be superior to anatomical methods of staging disease and therefore planning therapy. Examples include non–small cell lung cancer, lymphoma and oesophageal tumours.
- *Residual disease*: because purely anatomical methods for deciding on the viability of residual masses after treatment has been poor, metabolic imaging is proving extremely useful *e.g.*, post-treatment mediastinal lymphoma masses and testicular abdominal masses.
- *Detection of recurrences*: good examples include the confirmation and site of recurrent colo-rectal cancer after surveillance blood testing has detected a rise in circulating tumour (CEA) markers.
- *Measuring the response to therapy*: it is often important to know how effective initial treatment has been in order to plan future therapeutic strategies. The best example is assessing response following the initial course of treatment of Hodgkin's lymphoma, when poor early response indicates that supplemen-

tary neo-adjuvant therapy may be necessary for the desired effect.

- *To identify the site of disease*: identifying the site of disease may be important to plan surgery *e.g.*, for squamous cell cancers of the head and neck, to direct biopsy when the disease is heterogeneous, in soft tissue sarcomas, and to find the site of disease when the only sign may be a raised circulating tumour marker such as in thyroid cancer or teratomas.
- *To identify the primary tumour when secondary cancers are present*: it may be critical to discover the primary cancer when a patient presents with an enlarged lymph node, as in head and neck cancers where the primary tumour may be small, or alternatively when the presentation raises suspicion of a para-neoplastic syndrome.

Cardiology and Cardiac Surgery

At present there are three major indications for PET scans using two physiological measurements in clinical practice. The two measurements are (i) to measure the myocardial perfusion using [^{13}N]-ammonia (or ^{82}Rb from an on-site generator) and (ii) to measure myocardial viability (using [^{18}F]-FDG). There is increasing interest in a third measurement, cardiac innervation by studying myocardial receptors, which may have a greater role in the future. The three applications of these measurements are:

- in the diagnosis and assessment of the functional significance of coronary artery disease (CAD) usually when the SPECT scan is not definitive. However with the increasing use of medical therapy for treating CAD the quantification of myocardial blood flow and changes will become more important in the near future.
- in the assessment of the viability of ischaemic or jeopardised myocardium. This is important because the risks and benefits of medical treatments in advanced CAD are closely related to the presence and extent of viable but hibernating myocardium *versus* non–viable infarcted/scar tissue.
- during the work-up of patients who are being considered for cardiac transplantation (although this may be regarded as a subset of viability assessment). It is of such importance it is often considered separately from assessing viability. Due to the procedural

Table 1.1. US Centers for Medicaid and Medicare Services Indications and Limitations for PET scans[3].

Indication	Date Approved	Purpose
Solitary Pulmonary Nodules (SPNs)	Jan 1, 1998	Characterisation
Lung Cancer (Non Small Cell)	Jan 1, 1998	Initial staging
Lung Cancer (Non Small Cell)	July 1, 2001	Diagnosis, staging and restaging
Esophageal Cancer	July 1, 2001	Diagnosis, staging and restaging
Colo-rectal Cancer	July 1, 1999	Determining location of tumours if rising CEA level suggests recurrence
Colo-rectal Cancer	July 1, 2001	Diagnosis, staging and restaging
Lymphoma	July 1, 1999	Staging and restaging only when used as an alternative to Gallium scan
Lymphoma	July 1, 2001	Diagnosis, staging and restaging
Melanoma	July 1, 1999	Evaluating recurrence prior to surgery as an alternative to a ^{67}Ga scan
Melanoma	July 1, 2001	Diagnosis, staging and restaging; Non-covered for evaluating regional nodes
Breast Cancer	Oct 1, 2002	As an adjunct to standard imaging modalities for staging patients with distant metastasis or restaging patients with loco-regional recurrence or metastasis; as an adjunct to standard imaging modalities for monitoring tumour response to treatment for women with locally advanced and metastatic breast cancer when a change in therapy is anticipated.
Head and Neck Cancers (excluding CNS and thyroid)	July 1, 2001	Diagnosis, staging and restaging
Thyroid Cancer	Oct 1, 2003	Restaging of recurrent or residual thyroid cancers of follicular cell origin that have been previously treated by thyroidectomy and radioiodine ablation and have a serum thyroglobulin >10ng/ml and negative ^{131}I whole body scan performed
Myocardial Viability	July 1, 2001 to Sep 30, 2002	Covered only following inconclusive SPECT
Myocardial Viability	Oct 1, 2001	Primary or initial diagnosis, or following an inconclusive SPECT prior to revascularisation. SPECT may not be used following an inconclusive PET scan.
Refractory Seizures	July 1, 2001	Covered for pre-surgical evaluation only
Perfusion of the heart using ^{82}Rb	Mar 14, 1995	Covered for non-invasive imaging of the perfusion of the heart
Perfusion of the heart using [^{13}N]-NH_3	Oct 1, 2003	Covered for non-invasive imaging of the perfusion of the heart

Table 1.2. UK Intercollegiate Committee on Positron Emission Tomography Recommended Indications for Clinical PET Studies[4]. The evidence supporting this is classified as (A) Randomised controlled clinical trials, meta-analyses, systematic reviews, (B) Robust experimental or observational studies, or (C) other evidence where the advice relies on expert opinion and has the endorsement of respected authorities.

Oncology Applications	Indicated	Not indicated routinely (but may be helpful)	Not indicated
Brain and spinal cord	•Suspected tumour recurrence when anatomical imaging is difficult or equivocal and management will be affected. Often a combination of methionine and FDG PET scans will need to be performed. (B) •Benign versus malignant lesions, where there is uncertainty on anatomical imaging and a relative contraindication to biopsy. (B) •Investigation of the extent of tumour within the brain or spinal cord. (C)	•Assess tumour response to therapy (C) •Secondary tumours in the brain. (C)	
Parotid	•Identification of metastatic disease in the neck from a diagnosed malignancy. (C)		•Differentiation of Sjögrens Syndrome from malignancy in the salivary glands. (C) •Primary tumour of the parotid to distinguish benign from malignant disease. (C)
Malignancies of the oropharynx	•Identify extent of the primary disease with or without image registration. (C) •Identify tumour recurrence in previously treated carcinoma. (C)	•Pre-operative staging of known oropharyngeal tumours. (C) •Search for primary with nodal metastases. (C)	
Larynx	•Identify tumour recurrence in previously treated carcinoma. (C)	•Staging known laryngeal tumours. (C) •Identification of metastatic disease in the neck from a diagnosed malignancy. (C)	
Thyroid	•Assessment of patients with elevated thyroglobulin and negative iodine scans for recurrent disease. (B)	•Assessment of tumour recurrence in medullary carcinoma of the thyroid. (C)	•Routine assessment of thyroglobulin positive with radioiodine uptake. (C)
Parathyroid		•Localisation of parathyroid adenomas with methionine when other investigations are negative. (C)	
Lung	•Differentiation of benign from metastatic lesions where anatomical imaging or biopsy are inconclusive or there is a relative contraindication to biopsy. (A) •Pre-operative staging of non small cell primary lung tumours. (A) •Assessment of recurrent disease in previously treated areas where anatomical imaging is unhelpful. (C)	•Assessment of response to treatment. (C)	
Oesophagus	•Staging of primary cancer. (B) •Assessment of disease recurrence in previously treated cancers. (C)	•Assessment of neo-adjuvant chemotherapy. (C)	
Stomach	•No routine indication. (C)	•Assessment of gastro-oesophageal malignancy and local metastases. (C)	
Small bowel	•No routine indication. (C)	•Proven small bowel lymphoma to assess extent of disease. (C)	

Table 1.2. Continued.

Oncology Applications	Indicated	Not indicated routinely (but may be helpful)	Not indicated
Breast cancer	●Assessment and localisation of brachial plexus lesions in breast cancer. (Radiation effects versus malignant infiltration.) (C) ●Assessment of the extent of disseminated breast cancer. (C)	●Axillary node status where there is a relative contraindication to axillary dissection. (C) ●Assessment of multi-focal disease within the difficult breast (dense breast or equivocal radiology). (C) ●Suspected local recurrence. (C) Assessment of chemotherapy response. (C)	●Routine assessment of primary breast cancer. (C)
Liver: primary lesion			●Routine assessment of hepatoma. (C)
Liver: secondary lesion	●Equivocal diagnostic imaging (CT, MRI, ultrasound). (C) ●Assessment pre and post therapy intervention. (C) ●Exclude other metastatic disease prior to metastectomy. (C)		
Pancreas		●Staging a known primary. (C) ●Differentiation of chronic pancreatitis from pancreatic carcinoma. (C) ●Assessment of pancreatic masses to determine benign or malignant status. (C)	
Colon and rectum	●Assessment of recurrent disease. (A) ●Prior to metastectomy for colo-rectal cancer. (C)	●Assessment of tumour response. (C) ●Assessment of a mass that is difficult to biopsy. (C)	●Assessment of polyps. (C) ●Staging a known primary. (C)
Renal and adrenal	●Assessment of possible adrenal metastases. (C)	●Paraganglionomas or metastatic phaeochromocytoma to identify sites of disease. (C)	●Assessment of renal carcinoma. (C) ●Phaeochromocytoma – [^{131}I]-mIBG scanning is usually superior. (C)
Bladder	●No routine indication. (C)	●Staging a known primary in selected cases. (C) ●Recurrence with equivocal imaging. (C)	
Prostate			●FDG in prostate cancer assessment. (C)
Testicle	●Assessment of recurrent disease from seminomas and teratomas. (B)	●Assessment of primary tumour staging. (C)	
Ovary	●In difficult management situations to assess local and distant spread (C)		
Uterus: cervix	●No routine indication (C)	●In difficult situations to define the extent of disease with accompanying image registration. (C)	
Uterus: body	●No routine indication. (C)		
Lymphoma	●Staging of Hodgkin's lymphoma. (B) ●Staging of non-Hodgkin's lymphoma. (B) ●Assessment of residual masses for active disease (B) ●Identification of disease sites when there is suspicion of relapse from clinical assessment (C) Response to chemotherapy. (C)	●Assessment of bowel lymphoma. (C) ●Assessment of bone marrow to guide biopsy. (C) ●Assessment of remission from lymphoma. (C)	

Table 1.2. Continued.

Oncology Applications	Indicated	Not indicated routinely (but may be helpful)	Not indicated
Musculo-skeletal tumours	●Soft tissue primary mass assessment to distinguish high grade malignancy from low or benign disease. (B) ●Staging of primary soft tissue malignancy to assess non-skeletal metastases. (B) ●Assessment of recurrent abnormalities in operative sites. (B) ●Assessment of osteogenic sarcomas for metastatic disease. (C) ●Follow up to detect recurrence or metastases. (B)	●Image registration of the primary mass to identify optimum biopsy site. (C)	
Skin tumours	●Malignant melanoma with known dissemination to assess extent of disease. (B) ●Malignant melanoma in whom a sentinel node biopsy was not or can not be performed in stage II. (AJCC updated classification). (C)	●Staging of skin lymphomas. (C)	●Malignant melanoma with negative sentinel node biopsy. (B)
Metastases from unknown primary	●Determining the site of an unknown primary when this influences management. (C)		●Widespread metastatic disease when the determination of the site is only of interest. (C)
Cardiac Applications	**Indicated**	**Not indicated routinely (but may be helpful)**	**Not indicated**
	●Diagnosis of hibernating myocardium in patients with poor left ventricular function prior to revascularisation procedure. (A) ●Patients with a fixed SPECT deficit who might benefit from revascularisation. (B) ●Prior to referral for cardiac transplantation. (B)	●Diagnosis of coronary artery disease or assessment of known coronary stenosis where other investigations (SPECT, ECG), etc) remain equivocal. (B) ●Differential diagnosis of cardiomyopathy (ischaemic versus other types of dilated cardiomyopathy). (C) ●Medical treatment of ischaemic heart disease in high risk hyperlipidemic patients. (C)	●Patients with confirmed coronary artery disease in whom revascularisation is not contemplated or indicated. (C) ●Routine screening for coronary artery disease. (C)
Neuropsychiatry Applications	**Indicated**	**Not indicated routinely (but may be helpful)**	**Not indicated**
	●Pre-surgical evaluation of epilepsy. (B) ●Suspected recurrence or failed primary treatment of primary malignant brain tumours. (Most of these patients will have had MRI and CT with equivocal results). (B) ●Early diagnosis of dementia (especially younger patients and Alzheimer's disease) when MRI or CT is either normal, marginally abnormal or equivocally abnormal. (B)	●The grading of primary brain tumour. (B) ●Localisation of optimal biopsy site (either primary or recurrent brain tumour). (C) ●Differentiating malignancy from infection in HIV subjects where MRI is equivocal. (C)	●Diagnosis of dementia where MRI is clearly abnormal (C) ●Most instances of stroke. (C) ●Most psychiatric disorders other than early dementia. (C) ●Pre-symptomatic or at risk Huntingdon's disease. (C) ●Diagnosis of epilepsy. (C)