Positron emission tomography

A report by the

National Health Technology Advisory Panel

November 1990

Australian Institute of Health

POSITRON EMISSION TOMOGRAPHY

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This report was prepared by the National Health Technology Advisory Panel (NHTAP) and finalised by the interim Australian Health Technology Advisory Committee. Any comments or information relevant to the subject matter of the report would be welcome. Correspondence should be directed to:

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CONTENTS

EXECUTIVE SUMMARY

- Positron emission tomography (PET) is a high cost diagnostic imaging technology based on cyclotron-produced radioisotopes. It has been used in research for a number of years. In the USA, there is now an increasing trend toward its use as a routine clinical tool.

- Two Australian hospitals plan to establish PET units during 1991:

  - The Royal Prince Alfred Hospital plans to establish a PET unit in association with the National Medical Cyclotron Facility currently under construction at the hospital. The PET unit will have a capital cost of $A5M.

  - The Austin Hospital proposes to establish a PET unit incorporating a small dedicated cyclotron. The capital cost will be $A9M.

- There is evidence that PET provides relevant diagnostic information in several clinical applications including:

  - localisation of epileptic foci in candidates for refractory epilepsy surgery;

  - grading the degree of malignancy of cerebral gliomas;

  - distinguishing between recurrent glioma and radiation necrosis.

  - detection of coronary artery disease;

  - assessment of myocardial viability.

- In neurological applications, PET has been used in patient management at some overseas centres for some years, but there has been little comparison with alternatives, particularly single photon emission computed tomography (SPECT). In cardiac applications further studies are needed to determine whether PET has advantages for patient management and outcome in comparison with alternatives, particularly new SPECT techniques.

- The cost of PET per study depends largely on throughput. At a realistic throughput of 1200 studies per unit per year, the cost would be about $1,900 per study. Many patients would require two to three studies.

- Offsetting savings associated with the use of PET can be identified, but these are unlikely to amount to more than 30 per cent of costs.

- It is not considered that a sufficient case has yet been established for the routine use of PET as a clinical service in Australia. Further evaluation is needed of PET as a clinical tool,

but it is suggested that there could be some value in using the technology as a primary reference method in developing applications of lower cost techniques.

- Although Commonwealth funding has been sought for the operating costs of the two proposed PET units the approaches from the hospitals were made prior to the establishment of the Nationally Funded Centres Program by the Australian Health Ministers Advisory Council, and the proposals were not assessed on that basis.

- It is considered that, if one or both PET units are established:

  - the technology should be subject to a coordinated evaluation of clinical and cost benefits;

  - all patients scanned should be suitable for inclusion in evaluation protocols; criteria for the selection of patients for PET scans should be developed;

  - evaluations undertaken should include assessment of patient benefit from the use of PET in cardiac and neurological applications in comparison with alternatives, particularly SPECT in cardiac and glioma studies, and SPECT and magnetic resonance imaging (MRI) in epilepsy studies;

  - studies should be prospective and closely involve referring clinicians. An independent organisation with expertise in evaluation should also be involved;

  - regular reports on the evaluations should be sent to appropriate Commonwealth and State authorities and professional bodies;

  - no further units should be considered until the evaluations, including detailed cost benefit analysis, are completed.

INTRODUCTION

Positron emission tomography (PET) is a high cost diagnostic imaging technology not currently available in Australia. It is based on the use of positron-emitting radionuclides usually produced at a cyclotron. Like other nuclear medicine techniques, PET images physiological function rather than anatomy. The National Health Technology Advisory Panel (NHTAP) first considered PET in its report "Medical Cyclotron Facilities" prepared in 1984 in response to proposals for the introduction of cyclotron technology into Australia (1).

Australia's first medical cyclotron facility is currently being established by the Australian Nuclear Science and Technology Organisation (ANSTO) at Royal Prince Alfred Hospital in Sydney. It is expected to become operational in April 1991. It is intended that the cyclotron will produce nuclear medicine radioisotopes for sale to other hospitals as well as positron-emitting isotopes for use in a PET facility on site.

The Austin Hospital in Melbourne is also proposing to establish a PET facility. It will incorporate a small cyclotron dedicated to the production of radionuclides for PET. The two hospitals and ANSTO have formed a joint organisation (AUSTPAC) aimed at the cooperative introduction of PET into Australia. Both hospitals are seeking funding from the Commonwealth Government to cover operating and evaluation costs.

As a consequence of the AUSTPAC proposals, the Commonwealth Department of Community Services and Health sought the advice of the NHTAP on the clinical and cost effectiveness of PET. This report has been prepared in response to the Department's request. It updates the material on PET in the 1984 report.

ISSUES RAISED BY THE PROPOSED INTRODUCTION OF PET INTO AUSTRALIA

The proposed introduction of PET into Australia raises a number of issues which need to be considered by governments, the health professions and the community. These include:

- the value of the contribution PET can make to patient care, including:
  - the effectiveness of PET in its clinical applications;
  - the availability and effectiveness of alternative modalities;
  - the significance of the benefit to patients in each application;
  - the magnitude of costs as well as any cost savings to health care;
- the value of the contribution PET can make to Australian research,

- whether the funds required could be spent more effectively in some other area of health care;

- effect on the health care workforce;

- safety and regulatory issues.

DESCRIPTION OF PET, STATUS AND CLINICAL RELEVANCE

When a positron is emitted from an atomic nucleus, it can travel only a very short distance before it interacts with an electron. Both particles are annihilated, to produce two photons which move away from the point of interaction in approximately opposite directions. By detecting both photons simultaneously, a line can be defined on which the positron emitting source must lie.

In a PET study, a radiopharmaceutical labelled with a positron-emitting radionuclide is introduced into the subject by inhalation or injection. Many thousands of annihilation events are recorded by detectors mounted in a ring structure around the subject, for a series of cross-sectional slices through the anatomical region of interest. Tomographic techniques are used to analyse the data, producing both images and quantitative measurements of radiopharmaceutical uptake in each slice.

The radiopharmaceuticals most often used in PET are listed in Appendix 1. Types of installations are described in Appendix 2.

Since the first PET units were developed in the mid-1970's, there have been major improvements in the technology, for example in spatial resolution and in data handling. Equipment performance may now be close to its theoretical limits, although further improvements in software may be possible. About 200 PET units have been established worldwide. Most are used primarily in research.

The value of PET as a research tool was recognised early in its history, but its use as a routine clinical tool was slow to develop, in part because of the high cost and complexity of the cyclotron - PET combination. In 1984 the NHTAP considered that PET was largely a research tool (1). In 1985, the Medical Cyclotron Committee, set up to examine in detail the costs and benefits of an Australian medical cyclotron, agreed that PET was likely to develop as a research and diagnostic tool of great importance but its major influence in the immediate future would be in research (2).

More recently, there has been increasing interest in PET as a clinical tool, spurred in part by the availability of smaller, lower cost cyclotrons dedicated to PET, and automated systems for the production of PET radiopharmaceuticals. It has been recognized for some years that PET has limited but useful clinical applications in the management of refractory epilepsy and some brain tumours. Recently, the potential for more extensive usage has been opened up, with the development of new applications of PET in the diagnosis and management of heart disease.

PET is being used in routine clinical work as well as research in several centres in the USA. The US Health Care Financing Administration is considering a submission from the Society of Nuclear Medicine and the American College of Nuclear Physicians seeking Medicare reimbursement for applications in studies of heart disease, epilepsy and brain tumours.

In Australia, it is proposed (3) that PET would be used as a routine clinical tool in the following applications:

Cardiac

- detection of coronary artery disease;
- assessment of myocardial viability to assist in decisions on revascularisation and heart transplant;

Neurological

- localisation of epileptic foci in candidates for refractory epilepsy surgery;
- grading the degree of malignancy of cerebral gliomas;
- distinguishing between recurrent glioma and radiation necrosis.

The clinical applications of PET are considered in more detail in later sections of this report. A major issue to be addressed is whether lower cost technologies are available which are equally effective in these applications. The relevance of PET results to patient management is also examined.

AUSTRALIAN PROPOSALS FOR PET INSTALLATIONS

Royal Prince Alfred Hospital, Sydney

The Royal Prince Alfred Hospital (RPA) is proposing to establish a PET centre as part of the National Medical Cyclotron project. It is expected to commence operation in 1991/92. The PET centre would be integrated into existing nuclear medicine services and would be in a separate building from the cyclotron. Capital funding required to cover the cost of the PET camera and site costs would be $A5 million. The New South Wales Government has agreed to contribute $A2 million, and the hospital is raising the remainder.

The operating costs for the PET centre, amounting to nearly $A1 million a year when the centre is fully operational, are being sought from the Commonwealth Government. The costs include salaries for 11 additional staff members to operate the centre, as well as maintenance and consumables costs.

Initially the Centre at RPA would have one PET camera but allowance is being made in the plans for the possibility that a second PET camera will be purchased at a later date. The plans also provide for data transfer between a magnetic resonance imaging (MRI) Unit and the PET centre.

It is proposed that evaluations will be undertaken of PET applications in relation to coronary artery disease, epilepsy and brain tumour. The current expectation is that in the first year 50 per cent of PET camera time would be devoted to cardiac patients, 25 per cent to epilepsy patients and 25 per cent to brain tumour cases. In subsequent years about 20 per cent of camera time would be used for research (3).

Austin Hospital, Melbourne

The Austin Hospital proposes to establish a PET centre, including a PET camera and a small dedicated cyclotron, within its Department of Nuclear Medicine. It is scheduled to commence operation in July 1992. Capital costs are estimated at $A9M, of which $A1.4M would be derived from a Medicare Teaching Hospitals Equipment Grant, $A1.3M from the Austin Hospital, $A3.5M from a fund raising program run by the Hospital, and $A1.5M from the Health Department, Victoria. Operating costs are expected initially to be $A1.2M a year, rising to $A1.4M a year (1989 values) when the centre is fully operational, and are sought from the Commonwealth. These costs include salaries for 12 staff.

Provisionally, the hospital estimates that 40 per cent of the patient mix will be in the areas of epilepsy and other neurological applications, 40 per cent heart disease, and 20 per cent glioma and other applications. It is proposed that evaluations of the performance and cost-benefit of PET will be carried out in relation to the localisation of epileptic foci, assessment of the severity of coronary artery disease, and detection, quantification and assessment of the degree of malignancy of cerebral gliomas (3).

PET AND SPECT

In examining the need for PET in Australia, there is a need to consider whether alternatives are available which would have comparable effectiveness. Often the most suitable alternative will be single photon emission computed tomography (SPECT). This is a technique for providing cross-sectional images of physiological processes using gamma cameras, single-photon emitting radionuclides, and tomographic data processing techniques. The tracers used in SPECT include the cyclotron-produced isotopes gallium-67, thallium-201, and iodine-123. In recent years, a range of new radiopharmaceuticals for SPECT has been developed, based on the more readily available and lower cost isotope, technetium-99m.

In contrast to the situation with PET, SPECT is well established in Australia, and most major hospitals now have SPECT units. They rely on imported cyclotron-produced isotopes and reactor-produced technetium-99m generators.

As for PET, SPECT technology has undergone major improvements, and its intrinsic resolution (which relates to the performance of the equipment) is now comparable to that of PET. However, the resolution observed in clinical studies is poorer owing to the lower specificity of uptake of the tracers used. Unlike PET, SPECT cannot take advantage of 'biological' tracers, that is radiopharmaceuticals chemically

equivalent to or closely matching substances involved naturally in physiological processes.

In addition, SPECT has lower sensitivity than PET and is less suitable for quantitative studies. Nevertheless it is being used in several applications considered suitable for PET, such as epilepsy studies. The relative performance of the two modalities in these applications is dicussed below.

CARDIAC APPLICATIONS OF PET

Detection of coronary artery disease

Although the resolution of PET is too poor for direct imaging of coronary arteries, it can image and quantify myocardial perfusion (blood flow in the myocardium) with tracers such as nitrogen-13 ammonia, oxygen-15 water, or rubidium-82. Reduced blood flow in one or more segments of the myocardium indicates the presence of coronary artery disease.

Usually a partially blocked coronary artery can maintain blood flow to the myocardium while the patient is at rest, but as the severity of the blockage increases, the ability of the artery to increase flow when a demand is placed on the heart is increasingly impaired. The effect of arterial narrowings on myocardial perfusion is often only demonstrated under conditions of physical stress, induced either by exercise or pharmacologically (usually with dipyridamole) (4). In PET studies of coronary artery disease, myocardial perfusion is usually measured both at rest and after the administration of dipyridamole.

The conventional techniques for myocardial perfusion studies are planar and SPECT imaging with the radioisotope thallium-201. Recently, several technetium-99m compounds have been developed for planar or SPECT cardiac imaging and are awaiting approval by the US Food and Drug Administration (FDA). They are reported to give better image quality than thallium-201, their cost is lower, and they are likely to be more readily available. MRI can potentially be used for myocardial perfusion studies, but the technique is still in the investigational phase.

Results from several studies indicate that PET techniques have high sensitivity (95-98 per cent) and specificity (88-100 per cent) for the detection of coronary artery disease (5,6). There have been a few comparisons of the performance of PET and thallium-201 planar or SPECT techniques in this application (5,6). They indicate that PET and thallium-201 studies have similar sensitivity, PET may have slightly higher specificity, and PET may more accurately identify diseased vessels. However, values reported in the literature for the sensitivity and specificity of the thallium stress test vary widely (7,8).

In a submission to the NHTAP, the Cardiac Society of Australia and New Zealand has stated that non-invasive techniques currently used for the detection of coronary artery disease and ischemia have low sensitivity and specificity. The Society suggests that PET can offer a rapid and reliable means of excluding coronary artery disease, confirming

myocardial infarction, and assessing the extent of coronary artery disease (9). However, the American College of Cardiology considers that not enough studies have been done to support the use of PET in the diagnosis of coronary artery disease (10).

In summary, there is evidence that PET is an efficacious technique for the detection and assessment of coronary artery disease through myocardial perfusion studies, but it cannot directly image coronary arteries and cannot replace coronary angiography in decision-making on therapy. As yet it has not been documented that it would have marked advantages over the cheaper and more readily available planar and SPECT techniques for myocardial perfusion studies, particularly with the new technetium-99m radiopharmaceuticals. Given the high cost and complexity of PET, it would seem most inappropriate to include it routinely in the diagnostic workup of patients suspected of having coronary artery disease.

Assessment of potential response to revascularisation

When some cardiac patients are being considered for revascularisation by coronary artery bypass surgery or angioplasty, it can be important to determine whether improving blood flow is likely to improve cardiac function. The question arises particularly with patients who have had a myocardial infarction or have impaired left ventricular function. There is a need for techniques which can accurately determine whether ischemic myocardial tissue is viable and likely to respond to improved blood flow, or is irreversibly injured.

Conventionally, the viability of heart muscle has been assessed by means of thallium-201 stress-redistribution studies and gated blood pool scanning. In the thallium-201 technique, the radiopharmaceutical is injected while the patient is at rest or preferably during exercise or after administration of dipyridamole. Radionuclide uptake is measured soon after injection and again about four hours later. If a defect (region of reduced uptake) detected in the first measurement is still present in the second (a fixed defect), the corresponding myocardial tissue is considered to be irreversibly injured. If the defect is no longer present in the second measurement (a transient defect), the tissue is considered to be ischemic but viable.

The accuracy of thallium-201 stress-redistribution imaging in the assessment of myocardial tissue viability has been challenged (5). In two studies, a number of heart muscle segments showing fixed defects in thallium-201 redistribution studies reverted to normal after revascularisation (11,12).

Gated cardiac blood pool scanning is usually performed after injecton of red blood cells labelled with technetium-99m. It is used to determine left ventricular ejection fraction (a measure of the overall capacity of the heart muscle to contract), and to identify specific regions of myocardium with impaired contractile function (heart wall motion). There is some evidence that a combination of these studies and thallium distribution studies can give a reasonably good indication of tissue viability and capacity to respond to

revascularisation (11,12). In the future, MRI may also be used to assess wall motion abnormalities.

It has been suggested that PET assessment, based on a combination of blood flow and metabolism studies, is superior to conventional approaches in the assessment of tissue viability (13). In ischemic myocardium, glucose metabolism can be maintained or even increased by use of anaerobic processes. PET studies with fluorine-18-deoxyglucose (FDG) can provide images and quantitative measurements of myocardial glucose metabolism. Segments showing reduced blood flow and reduced glucose metabolism are considered to be irreversibly injured, while segments with reduced blood flow and normal or increased FDG uptake are considered to represent viable myocardium.

There is evidence that PET blood flow/glucose metabolism studies can predict the outcome of revascularisation more accurately than thallium-201 scintigraphy, although the numbers of patients in studies reported in the literature were small, and outcome was assessed in terms of technical parameters rather than patient symptoms and quality of life.

In a study of 17 patients who underwent coronary artery bypass surgery, PET was used to predict whether pre-operative abnormalities in left ventricular wall motion would be reversed by revascularisation (14). Abnormal wall motion in regions in which PET images showed preserved FDG uptake was predicted to be reversible, whereas abnormal motion in regions with depressed FDG uptake was predicted to be irreversible. The predictions were correct for 35 of the 41 segments with abnormality predicted to be reversible (85 per cent positive predictive accuracy), and 24 of the 26 regions predicted to have irreversible injury (92 per cent negative predictive accuracy). By contrast with previous studies (11,12), no correlation was found between the severity of wall motion abnormality and the degree of post-operative improvement.

In a study of 31 patients, PET with nitrogen-13 ammonia blood flow studies alone was found to predict response to revascularisation more accurately than thallium-201 redistribution (15).

In a study of 20 patients, blood flow and FDG uptake were examined in myocardial regions with electrocardiographic evidence of transmural myocardial infarction. In 68 per cent of Q-wave regions, blood flow was either normal or reduced, but FDG uptake was maintained, while blood flow and FDG uptake were concordantly reduced in only 32 per cent of the regions (16).

PET studies with nitrogen-13 ammonia and FDG were compared with thallium-201 SPECT in a study of 26 patients. Of the 142 myocardial segments analysed, 101 had fixed defects on SPECT, 31 had partially reversible defects, and ten had completely reversible defects. Preserved glucose utilisation was identified in 47 (46.5 per cent) of the segments with fixed defects and 20 (64.5 per cent) of the segments with partially reversible defects. The results suggested that the extent of tissue viability in patients with ischemic heart disease was underestimated by thallium-201 SPECT (17).

In a study of 13 patients with acute myocardial infarction, myocardial blood flow and glucose metabolism were evaluated within 72 hours of the onset of acute symptoms. Of 32 segments in infarct regions, 16 revealed increased FDG uptake and reduced blood flow in comparison with unaffected tissue, whereas in the other 16 segments FDG uptake and blood flow were concordantly reduced. On re-examination six to ten weeks later, all regions with blood flow-glucose metabolism 'matches' continued to have impaired function. In the 16 segments with blood flow-metabolism 'mismatches', function had improved spontaneously in eight. It was suggested that the 'mismatch' pattern represents 'stunned' rather than irreversibly injured myocardium (13).

Overall the results of these studies indicate that PET would be more accurate than conventional thallium-210 redistribution scintigraphy in the assessment for revascularisation of patients with an old myocardial infarction, a recent myocardial infarction, or impaired left ventricular function. It is not clear how significant the advantage would be in the total clinical assessment of the patient.

The Cardiac Society of Australia and New Zealand considers that no other technique offers such a precise degree of separation of ischemic but viable heart tissue from irreversibly damaged myocardium (9). The American College of Cardiology considers that PET is useful in determining the viability of diseased heart tissue for patients who are candidates for bypass surgery or coronary angioplasty, when other evaluations fail (10).

Early results suggest that a modification of the thallium-201 test involving reinjection of thallium after stress-redistribution imaging might be comparable to PET in the assessment of myocardial viability. Twenty patients who had received the new test before coronary angioplasty were re-examined three to six months after the procedure. Of the 15 myocardial regions with defects on redistribution that were identified as viable by reinjection studies, 13 (87 percent) had normal thallium uptake and improved regional wall motion after angioplasty. In contrast, all eight regions with persistent defects on reinjection imaging before angioplasty had abnormal uptake and abnormal regional wall motion after angioplasty (18). These results need to be confirmed in larger studies before this technique can be considered an alternative to PET in the assessment of myocardial viability.

While at this stage conventional MRI cannot be used to assess the viability of ischemic myocardial tissue, in the future magnetic resonance spectroscopy may be able to do so through biochemical metabolic studies. However, its development in this application is well behind that of PET and it is likely to be more expensive and difficult to use.

Other cardiac applications

It is sometimes uncertain whether a stenosis detected by coronary angiography is responsible for the symptoms experienced by the patient. In the past, thallium-201 scintigraphy has been used to

assess the physiological significance of such stenoses. It is possible that PET could provide a more reliable assessment.

Without coronary angiography, it can be difficult to determine whether dilated heart failure is due to coronary artery disease or is idiopathic. It has been suggested that it would be desirable to have a 'non-invasive' technique capable of discriminating between ischemic and non-ischemic conditions (5). There is evidence that PET studies of fatty acid metabolism with carbon-11 palmitate (19) as well as blood flow and metabolism studies (13) can distinguish these conditions.

PET is used in at least one institution in the USA in the assessment of patients referred for cardiac transplantation. A number of potential candidates for transplantation have been submitted instead to surgical revascularisation after PET demonstrated the presence of a large fraction of viable myocardium in the left ventricle (13).

Potential impact of cardiac applications of PET in Australia.

Both the Royal Prince Alfred and Austin Hospitals propose to devote a substantial amount of PET camera time to clinical cardiac studies. The Royal Prince Alfred Hospital proposes to use PET in the assessment of coronary artery disease, selection of patients for coronary artery bypass surgery or angioplasty, and assessment of patients for cardiac transplantation. The assessment of coronary artery disease by PET would apply particularly to patients with chest pain of uncertain etiology, those with recurrent symptoms following surgery, and those with left ventricular dysfunction being considered for surgery. The Hospital considers that the use of PET may obviate the need for coronary angiography in some of these patients.

The Austin Hospital proposes to use PET in the assessment of patients admitted with acute chest pain. The Hospital has suggested that the use of PET will reduce the length of time in coronary care by an average of one day each for patients with definitive ischemia, and reduce the numbers of exercise ECT tests, exercise thallium-201 studies, and coronary angiograms. These suggestions are examined in the section of this report on potential off-setting savings.

The presence of one or two PET installations in Australia could stimulate pressure from other hospitals for the installation of PET for cardiac applications, based on generator-produced positron-emitting radionuclides, and FDG supplied from the cyclotrons at Royal Prince Alfred and Austin Hospitals. Such installations would be very limited in the scope of the studies they could undertake, and could experience supply difficulties, but they would enable wider application of PET in the detection of coronary artery disease.

It is difficult to conclude that there would be justification for the widespread use of such a high cost and complex modality in the detection of coronary artery disease. At this stage there is little evidence that PET would be more accurate in the detection of disease than a combination of clinical assessment of signs and symptoms, and existing non-invasive tests.

There is a better case for the use of PET in the assessment of tissue viability and response to revascularisation in selected patients. However, there is a need for an evaluation of this application under routine clinical conditions. Ideally, the evaluation would take the form of a randomised controlled trial. Patients with a previous myocardial infarction or impaired left ventricular function, who are under consideration for revascularisation, would be randomised between two groups. One group would have PET included in their assessment, the other would not. Data would be collected on the numbers of patients who proceed to revascularisation, and on outcomes including technical measures of function, recurring symptoms and quality of life. It would be desirable for the protocol which excluded PET to incorporate thallium-201 reinjection imaging.

It has been claimed that PET usage can result in the avoidance of ineffective revascularisation procedures. If PET is used instead of conventional thallium-201 stress-redistribution imaging in the assessment of patients for revascularisation, it could result in an increase in the number of revascularisation procedures, since thallium-201 techniques are said to underestimate tissue viability (17). However, it would be very difficult to gauge the potential effect of PET on numbers of revascularisation procedures without detailed information on current practices in the management of the relevant patients. These are likely to differ from hospital to hospital.

There may be a case for the use of PET in the assessment of candidates for cardiac transplantation. Again, an evaluation is needed, focusing on the outcomes of patients referred for revascularisation rather than transplantation. The impact of PET on cardiac transplantation would not be expected to be substantial, given that selection of patients for these procedures is already very rigorous.

NEUROLOGICAL APPLICATIONS OF PET

PET in the management of epilepsy

Epilepsy patients whose seizures cannot be controlled by medication may be considered for surgery, provided that the seizures originate from a localised area of the brain (refractory focal epilepsy). Usually, the epileptic foci of patients submitted for surgery are in the temporal lobes.

Before patients with refractory epilepsy are submitted to surgery, they undergo evaluation to determine whether surgery is appropriate, and to localise the epileptic foci as precisely as possible. This is a complex process requiring multiple diagnostic procedures, as no single test provides sufficient information to guide the surgeon. The mix of techniques used will differ from institution to institution, but typically they include prolonged surface electroencephalographic recording (EEG) combined with video monitoring of the patient, and EEG with intracranial electrodes.

PET has been used for some years to assist in the localisation of foci during pre-surgical evaluation. In PET studies, changes in blood flow

and particularly metabolism are used to identify epileptic foci. During seizures, both metabolism and blood flow are greatly increased in the region of the foci, whereas in the period between seizures they are reduced relative to normal tissue. Owing to the logistic difficulties of making short-lived isotopes available at the unpredictable times of seizures, PET studies are usually performed in the periods between seizures.

Published comparisons with intracranial electrode EEG and pathological examination of resected specimens indicate that PET has a sensitivity of about 70 per cent in the detection of epileptic foci (20). The Panel was advised that with state of the art PET, foci are correctly localised in 85 per cent of cases studied at the University of California at Los Angeles (Burkovic, personal communicaton).

Addition of PET to the techniques used in pre-surgical evaluation may reduce the need for intracranial electrode EEG, which is invasive, painful, and carries some risk of infection. There appear to be no firm data on the extent of the reduction, but the opinion has been expressed that in the Comprehensive Epilepsy Program at the University of California at Los Angeles, the introduction of PET has reduced the need for intracranial EEG by 30-50 per cent (21).

PET studies of opiate and benzodiazepine receptors with carbon-11 labelled radiopharmaceuticals have shown that epileptic foci have reduced receptor density. The use of these techniques to provide images of foci could increase sensitivity but further studies are needed to determine their clinical usefulness (20,22).

There is increasing use of SPECT in the pre-surgical evaluation of epilepsy patients (23,24,25). While this technique is currently restricted to blood flow studies for the localisation of epileptic foci, it has the advantage that it is easier to use than PET during seizures or immediately after them. Such studies must be undertaken as in-patient procedures during patient monitoring. In recent Australian work, SPECT used with technetium-99m hexamethylpropyleneamine oxime (Tc-99m HMPAO) immediately after seizures has given promising results with epileptic foci correctly localised in 73 per cent of cases (24). SPECT studies between seizures can be performed on an outpatient basis but are inaccurate (24,25).

The General Advisory Committee of the Australian Association of Neurologists has advised that it is unaware of any reliable comparative data on PET and other techniques such as SPECT in the investigation of patients with epilepsy, stroke and other neurological disorders (26). At this stage, it is too early to judge whether SPECT is an equally effective alternative to PET in the assessment of refractory epilepsy patients, but the requirement for in-patient use would give it a practical disadvantage.

MRI and computed tomography (CT) may also be used in the pre-surgical evaluation of epilepsy patients. Their primary role is to assist in the delineation of structural abnormalities. However, in a high proportion of cases, CT gives normal scans (27). The use of MRI has given mixed results although in recent Australian work there have been

promising findings (28). These technologies have generally not been considered as alternatives to PET in this application, although they have important roles in the initial diagnostic investigations of epilepsy patients.

Magnetoencephalography or biomagnetometry is a technology which could have a significant role in the future in the localisation of epileptic foci, but as yet is still in the investigative stage. It is based on the measurement of the extremely weak magnetic fields generated by the electrical currents within the brain.

PET in the management of cerebral gliomas

AUSTPAC has proposed that in the management of cerebral gliomas, PET can be used to establish the degree of malignancy of the tumours, differentiate tumour from edema, distinguish recurrent tumour from radiation necrosis, and assess sensitivity to chemotherapy (3).

It has been known for some years that the level of glucose metabolism in a cerebral glioma, as determined by PET measurement of FDG uptake, correlates well with the degree of malignancy of the tumour (29). It can also be used as a predictor of the patient's survival period (30). Information on degree of malignancy and projected survival period have an important influence on decisions on therapy. With high grade malignancies, life expectancy is usually very short and further therapy likely to be useless. With low grade malignancies life expectancy can be much longer.

Other techniques available for determining the malignancy grade of gliomas include stereotactic biopsy, CT and thallium-201 SPECT. Stereotactic biopsy would appear to be the 'gold standard' technique but sampling errors can occur if the tumour is of a mixed type (31). Both PET and SPECT could help to reduce sampling errors through assisting in the localisation of any parts of the tumour with high-grade characteristics.

High grade malignancies can be distinguished from low-grade tumours in the majority of cases by plain and contrast CT studies. With high grade tumours there is marked contrast enhancement, while with low grade tumours the use of contrast medium usually gives little or no change in the image (30). However, there is evidence that CT is less accurate than PET in the grading of low activity lesions (29). While MRI is an accurate technique for the detection of gliomas, it has been less successsful in determining their grade (32), although it is possible that better results will be obtained with new paramagnetic contrast agents.

Thallium-201 SPECT can also be used to distinguish high and low-grade cerebral gliomas, on the basis of thallium-201 uptake. An accuracy of 89 per cent has been reported for this technique. According to one study it gave better results than CT (31).

Gliomas are treated by surgery, chemotherapy and radiotherapy. In the course of evaluating the response to therapy it can be difficult to

distinguish between residual or recurrent tumour and edema or radiation necrosis. These distinctions cannot reliably be made with CT, or nuclear medicine techniques based on radionuclides such as technetium-99m and gallium-67. However, it has been established that PET with FDG or tracers labelled with carbon-11 can accurately differentiate tumour from edema and necrosis (20,33,34).

Evidence based on limited numbers of patients suggest that thallium-201 SPECT may be an alternative to PET in the differentiation of tumour for radiation necrosis and edema (31,35). At this stage, however, there has been very little direct comparison of the SPECT technique with PET in these applications. Paramagnetic contrast agents have substantially improved the capacity of MRI to distinguish between tumour and edema (36).

The General Advisory Committee of the Australian Association of Neurologists has commented that the importance of PET in these applications requires further evaluation (26).

Through its capacity to measure metabolism, PET can provide unique information on the early response of brain tumours to chemo- or radiotherapy (37). The clinical usefulness of the results has not been established, and this application of PET remains in the research area.

Other neurological applications of PET

There are a number of other neurological applications of PET which have uncertain value in patient management owing for example to the absence of effective therapy, or which lie in a 'grey' area between research and clinical utility.

In studies of stroke patients, PET can provide an indication of tissue viability in the affected region of the brain. In the past it was suggested that the information from PET studies could assist in selecting patients for surgical intervention (endarterectomy or extra-cranial intra-cranial bypass) (20). It seems that there is now less enthusiasm for these procedures in stroke cases. The Royal Australasian College of Radiologists has suggested that quantitative blood flow and cerebral metabolism studies with PET may become particularly valuable with the advent of acute fibrinolytic therapy for cerebral infarction (38).

It has been suggested that the results of PET studies could assist in the selection of stroke patients for rehabilitation programs (3). The suggestion should be regarded with caution. It would seem inappropriate to deny a patient access to rehabilitation on the basis of a PET scan, if it has been indicated by clinical assessment.

In the area of the dementias, PET can differentiate Alzheimer's disease, multi-infarct dementia and reversible dementia (induced by depression or medication) more reliably than CT or MRI (39,40). Given the current absence of effective therapy for the irreversible dementias, the clinical usefulness of diagnostic imaging in these cases is unclear, except perhaps in the identification of reversible dementia in cases where clinical assessment gives equivocal results.

PET has been used in studies of movement disorders, particularly Parkinson's Disease. It has been suggested that PET studies could assist in decisions on therapy in some cases (3). It is not clear however that this application has fully emerged from the investigational phase.

It has also been suggested that PET can assist in the diagnosis of Huntingdon's Disease at an early stage, so that genetic counselling can be given (3). It is noted that there is debate as to whether PET can detect asymptomatic Huntingdon's Disease carriers (39).

It has been suggested that PET might assist in the diagnosis of schizophrenia, distinguishing it from other acute psychiatric disorders (3). However, PET studies of glucose metabolism in schizophrenic patients have given conflicting results, possibly reflecting the heterogeneous nature of the disorder (39). While PET studies of schizophrenia are of major importance in developing understanding of this condition, they remain in the investigational category.

Potential impact of neurological applications of PET in Australia

Management of epilepsy patients

It is estimated that in Australia nearly 6000 new cases of epilepsy are diagnosed each year. Of these, about 7 per cent or at least 420 cases would be suitable for pre-surgical assessment at some stage in the course of their disease (41). In practice the numbers currently being assessed are much lower, although they are expected to increase as the treatment becomes more widely known. There would also be a substantial backlog of patients potentially suitable for assessment.

Four hospitals in Sydney, two in Melbourne, three in Adelaide and one in Perth undertake these assessments. The great majority of cases are assessed in Sydney and Melbourne.

Data from the Prince Henry and Austin Hospitals supplied to the Australian Institute of Health indicate that about 80 per cent of patients referred for surgical assessment proceed to detailed investigations. Of these about 50 per cent undergo intracranial EEG. About 50 per cent of the patients evaluated finally proceed to surgery. Intracranial electrodes are used in 66 per cent of these cases.

If PET units are installed in Sydney and Melbourne it seems likely that the majority of patients in these cities being assessed for surgery will receive PET although neither the Austin nor the Royal Prince Alfred Hospitals have indicated whether referrals from other hospitals would be encouraged.

The Austin Hospital has proposed that a PET scan should be the first step in the pre-surgical assessment program after clinical assessment and standard radiographic examinations. If epileptic foci can be localised by PET and the locations are confirmed by ictal surface EEG, the patient would proceed to surgery. If not, SPECT would be

performed. If the locations of the foci are still not confirmed, depth electrodes would be used.

The Royal Prince Alfred Hospital also plans to use PET in the pre-surgical assessment of refractory epilepsy patients but has not specified its role in relation to other modalities.

Both hospitals believe that the introduction of PET would result in reduction in the use of intracranial electrodes and the Austin Hospital has noted that a number of SPECT studies would also be replaced.

It is noted that the development of SPECT techniques in this application will have already reduced the use of intracranial EEG to some extent. The addition of PET to a program which already includes SPECT might result in some further reduction in the use of the intracranial technique but it is suggested that the further reduction is unlikely to be more than 40 per cent. The reduction in the use of SPECT might be of a similar magnitude. There would be an associated reduction in the period of hospitalisation required for assessment.

Management of cerebral glioma

In 1982 899 persons in Australia were newly diagnosed to have cancer of the brain or nervous system (42). Probably 80 per cent of these cases would have been cerebral gliomas. If population increase since 1982 is allowed for, the annual incidence of new cases of cerebral glioma is likely to be in the region of 800.

At currently envisaged rates of usage, the two proposed PET units would perform 400-500 examinations a year related to cerebral glioma.

The Royal Prince Alfred Hospital has suggested that the use of PET in the management of glioma will reduce the number of operations, re-operations and biopsies. The Austin Hospital considers that biopsies would be bypassed (3). While it seems likely that the use of PET in the management of these patients would result in some reduction in the number of procedures performed, it is felt that it would be unlikely that biopsies would be replaced altogether.

General

The Australian Association of Neurologists has noted that the full potential of PET is not yet known but it is likely to find increasing application in refining neurological diagnosis and management. The Association suggests that it would seem reasonable to have PET units in a small number of major centres in Australia (26). On the other hand the Royal Australasian College of Radiologists considers that while PET has a role in clinical medicine and research, it should have a lower priority than MRI (38).

RESEARCH APPLICATIONS

The variety of physiological processes which can be traced with PET and its capacity for quantitation make it a powerful research

tool. At the same time it has limitations, notably its relatively low spatial resolution, and the need in some studies to ensure rigorously standardised conditions even with regard to the mental activities of the patient.

In this report the research applications of PET are not comprehensively reviewed, but some examples are given below to indicate their range.

PET continues to be used in studies of the normal brain, for example in the localisation of specific functions (43,44). In studies of abnormal brain states, a major area of research is schizophrenia. PET is being used to seek an understanding of biochemical abnormalities related to the disease, identify subtypes of schizophrenia, and study the mechanisms of drug action. The research involves studies of both glucose metabolism and dopamine receptors (39).

In the area of the dementias, PET may be able to contribute to an understanding of the biochemical basis of Alzheimer's disease, and identify subtypes (45,46). PET is being used in studies related to drug addiction, for example in studies of the effects of cocaine on the brain's metabolism and neurotransmitter systems (47).

In addition to clinical applications in relation to heart disease, PET is making a useful contribution to research on the heart. For example, PET is being used to study the metabolic factors underlying dilated cardiomyopathy (48). Neuronal activity in the heart is being studied with carbon-11 hydroxyephedrine. Evidence has been found that renervation starts to occur in a transplanted heart some time after transplant, and areas of denervation after myocardial infarction have been shown. It might become possible to use the technique to identify a risk of life-threatening cardiac arrhythmias (Schwaiger, personal communicaton).

In the future, PET may have wider application in the area of oncology. For example, it may be used to grade the degree of malignancy of tumours other than cerebral gliomas (49). It has been used to differentiate recurrent colorectal tumour from scar (50). A radiolabelled estrogen analogue has been used in PET studies of primary and metastatic breast cancer The technique might be helpful in guiding antiestrogen chemotherapy (51).

In Australia, the most useful research application of PET may well be as a primary reference method in developing applications of lower cost techniques. For example, it would be particularly useful to compare SPECT and PET in the localisation of epileptic foci. It would also be useful to compare PET and SPECT with technetium derivatives in myocardial perfusion studies. If such studies were being done overseas there would be little point in duplicating them in Australia. However, it appears that very little work of this kind is being done overseas.

COSTS OF PET

The capital and operating costs at full operation (60 hour week) for the two PET units proposed are summarised in Table 1. The capital cost

of $5M for the Royal Prince Alfred Hospital unit covers the PET camera, ancillary equipment and site costs, but does not include a component of the cost of the medical cyclotron facility (totalling $16.4M, to be met by ANSTO). Although the cyclotron is being constructed in any case, and is not being funded from health care budgets it was considered that it cannot be omitted from the costing of PET. The cyclotron cost component was estimated to be $661,000 (one third of annualised capital cost, operation and maintenance cost).

The capital cost of $9M for the unit at Austin Hospital covers the PET camera with ancillary equipment, a small cyclotron dedicated to the production of radioisotopes for PET, and site costs.

Both hospitals have provided estimates of development activities which include costs associated with setting up the projects and staff training. To a considerable extent, these costs have already been incurred.

The NHTAP estimated annualised capital (and development) costs on the basis of the following assumptions:

- the PET camera is depreciated over seven years, minor equipment and development costs over 10 years, the cyclotron (at Austin Hospital) over 15 years, and site costs over 25 years;
- there is no residual value;
- no allowance is made for the opportunity cost of the capital;
- no allowance is made for return on investment.

TABLE 1: CAPITAL AND OPERATING COSTS OF PET

	$million
Royal Prince Alfred Hospital	
Capital cost	5.00
Development cost	0.50
Annualised capital cost	0.66
Annual operating cost (full operation)	0.96
Cyclotron component	0.66
Total annual cost	2.28
Cost per study	$2,850 (800pa)
	$1,900 (1200pa)
	$1,520 (1500pa)
Austin Hospital	
Capital cost	8.96
Development cost	1.26
Annualised capital cost	0.94
Annual operating cost (full operation)	1.39
Total annual cost	2.33
Cost per study	$2,910 (800pa)
	$1,940 (1200pa)
	$1,550 (1500pa)

Sources: AUSTPAC Submission
NHTAP Estimates

The hospitals expect to achieve full operation in the third year after start-up. Table 2 gives estimates of operating costs over the first three years. They are based on hospital costs but do not include their figures for staff travel and technology evaluation. The major components of operating costs are staff salaries and equipment maintenance. Table 3 lists staff requirements proposed by the hospitals at operation for 40 and 60 hours a week respectively.

Cost estimates in this report are based on the hospitals' estimates of staff requirements. However, staffing requirements may be overestimated for clinical use. In particular, it is difficult to see why three to 3.5 medical practitioner positions would be required for the unit at The Royal Prince Alfred Hospital, other than for research or why three to four nuclear medicine technologists would be required full-time at The Austin Hospital. Nursing and orderly requirements are also believed to overestimated, unless scheduling problems mean that patients spend lengthy periods of time in the PET unit.

TABLE 2: OPERATING COSTS OF PET

Royal Prince Alfred Hospital	**Costs ($'000)**		
	First year	Second year	Third year
Staff salaries	540	627	627
Maintenance of equipment	10	185	185
Goods and services	50	60	75
Indirect costs	65	75	75
TOTAL	755	946	961
Austin Hospital			
Staff salaries	513	549	674
Maintenance of equipment	438	438	438
Supplies (general, medical, cyclotron)	60	60	90
Electricity	56	56	84
Building maintenance	18	18	18
Indirect costs	61	66	81
TOTAL	1,146	1,187	1,385

Source: AUSTPAC submission (with amendment)

TABLE 3: HOSPITAL ESTIMATES OF STAFF REQUIREMENTS FOR PET UNITS

Royal Prince Alfred Hospital	40 hours/wk	60 hours/wk
Physicians	2.0	2.0
Registrars	1.0	1.5
Physicists	2.0	2.0
Radiopharmacist	1.0	1.0
Chemist	1.0	1.0
Nuclear medicine technologists	2.0	3.0
Nurse	1.0	1.5
Secretary	1.0	1.0
Austin Hospital		
Physicians	1.0	1.5
Physicists	2.0	2.0
Radiochemists	2.0	2.0
Nuclear Medicine Technologists	3.0	4.0
Administrative Assistant	1.0	1.0
Nurses	1.2	1.8
Orderlies	1.2	1.8

Source: AUSTPAC Submission

Both hospitals have proposed specific programs of evaluation of the clinical applications of PET. These would require the appointment of data managers, development of evaluation protocols and measures of patient outcome, and cost benefit analysis. Allowance for evaluation is not included in the estimates of operating costs given in this report as it was considered that evaluation should be funded separately. The Panel's estimates of evaluation costs are given in Table 4.

TABLE 4: ESTIMATED EVALUATION COSTS FOR TWO PET UNITS

ITEM	COST $
Capital Cost	
Computer/software (two packages)	24,000
Cost at each hospital per annum	
Data manager	45,000
Registrar (half time)	27,000
Secretary (half time)	12,000
Cost at coordinating centre	
Data analyst (half time)	23,000
Secretarial/publishing	5,000
Annual evaluation cost	**204,000**

Note: The registrar position included in this estimate would already be covered in the hospitals' estimates of staff requirements and would not be additive to those estimates.

The cost of PET per examination will depend on throughput. The Hospitals expect that in the first year throughput will be low (200-360 studies a year). In the second year it is expected to rise to 750-800 and in the third year to 6-8 studies a day (Royal Prince Alfred Hospital) or 1500 a year (Austin Hospital).

The Panel estimated costs per studies at throughputs of 800, 1200 and 1500 a year. These are given in Table 1. In the Panel's view, it could be optimistic to expect a throughput of 1500 a year, given the complexity of the procedure, but a throughput of 1200 a year should be readily achievable.

If two PET cameras were operating at Royal Prince Alfred Hospital, and throughput were doubled, cost per study would be less since not all costs would be doubled. At a throughput of 2,400 a year, cost per study is estimated to be $1,500.

It should be noted that the throughput estimates refer to studies, not patients. Many patients would require two to three studies. For example, a patient undergoing assessment of myocardial viability would require a blood flow study and a glucose metabolism study.

The cost of PET can be placed in perspective by considering alternative uses for the funds required. For example, the annual operating cost of a PET unit at Royal Prince Alfred Hospital would be equivalent to the cost of around ten hospital beds (including nursing, catering, cleaning and administration). The operating cost for the PET unit at Austin Hospital would be equivalent to around fourteen hospital beds, or a quite substantial community health centre.

The capital and operating costs of PET at the Austin Hospital would be substantially reduced if the unit did not incorporate a cyclotron (see Appendix 2). At least in theory, it would be possible for FDG to be supplied from the cyclotron facility in Sydney, and it may also be possible to import generator systems, particularly rubidium-82 generators. While the studies possible with PET under this arrangement would be restricted, the restriction would be less significant for a unit engaged primarily in routine clinical applications than one used mainly for research. The availability of FDG would permit studies of epileptic foci, brain tumours, and myocardial metabolism, and rubidium-82 could be used for myocardial perfusion studies.

The disadvantages of such a mode of operation would include the logistic difficulties of supplying FDG from Sydney (see Appendix 2), the vulnerability of the supply to transport disruptions, the problems of dependence on another organisation, the high cost of rubidium-82 generators (in the USA a generator with a lifetime of 6 weeks costs $US25,000), and possible unreliability in generator supply. In addition, throughput would be severely restricted, increasing cost per patient.

Very approximate estimates of the costs for a PET unit without a cyclotron at Austin Hospital are given in Table 5. It is assumed that capital and development costs would be similar to those for the unit at Royal Prince Alfred Hospital, except that site costs should be

lower. In estimating operating costs, it was assumed that staff would be reduced, with no need for chemists and with a reduced need for other support staff. Equipment maintenance would also be reduced. To some extent the savings in these areas would be counterbalanced by the costs of purchasing FDG (cost estimated to be $250 a day, or $56,000 a year) and rubidium-82 (cost estimated to be $264,000 a year).

The availability of cyclotron facilities in Sydney and Melbourne could lead to a demand for PET units at other hospitals in these cities. They could readily be supplied with fluorine-18 radiopharmaceuticals, and possibly some other positron-emitting tracers, from the cyclotrons at Royal Prince Alfred and Austin Hospitals. The costs for each unit could be in the region of those given in Table 5. Operating costs may be reduced if rubidium-82 is not purchased.

TABLE 5: CAPITAL AND OPERATING COSTS OF A PET UNIT WITHOUT A CYCLOTRON

Capital costs		**$M**
PET camera		3.38
Minor equipment		0.25
Site costs		0.50
Total		4.09
Development costs		0.50
Annualised capital and development costs		0.56
Operating costs		
Staff		0.325
Equipment maintenance		0.185
Supplies (including FDG, rubidium-82)		0.380
Building maintenance		0.015
Indirect costs		0.075
Total		0.98
Total annual costs		1.54
Cost per examination		**$**
- throughput	400pa	3,800
	800pa	1,900
	1200pa	1,300

Note: The throughput range used in this estimate is lower than for Table 1 as operation without a cyclotron will restrict throughput.

POTENTIAL OFF-SETTING COST SAVINGS

Cardiac applications

It has been suggested that in cardiac applications, the use of PET would result in off-setting cost savings through the avoidance of coronary angiography, replacement of thallium stress tests and exercise ECG, reduction in time spent in coronary care, and avoidance of unnecessary or ineffective surgery (3).

In the assessment of patients suspected of having coronary artery disease, PET might reduce the number of patients referred to coronary angiography if its specificity were higher than that of the combination of all currently used non-invasive techniques. To give an indication of the savings which might be involved they have been estimated for a hypothetical situation as follows:

- 500 patients a year are examined by PET to detect the presence of coronary artery disease (estimated to be half the total number of cardiac examinations for the two PET units);
- the specificity of PET in the detection of coronary artery disease is 88-100 per cent;
- the specificity of the combination of alternative non-invasive technique (ECG, exercise ECG, thallium stress test) is 75-85 per cent;
- the patient population is well selected, and the probability of the presence of disease is 60-80 per cent;
- all cases identified as positive by the non-invasive tests are referred for coronary angiography;
- the cost of a coronary angiogram is $2,100, including hospitalisation required.

On the basis of these assumptions the use of PET would reduce the numbers of false positive cases by 3-50, and the cost savings through avoidance of coronary angiograms would be in the range $6,300-105,000. It is emphasised that this estimate is based on a model only and gives only an indication of the order of magnitude of any savings. An accurate estimate would require much more data than are available.

The Austin Hospital has suggested that for patients admitted with acute chest pain, the use of PET could reduce the time spent in intensive care as it would result in more rapid diagnosis, avoidance of other tests, and more rapid allocation of patients to appropriate treatment streams. The Hospital has estimated that an average saving of one day per patient could be achieved (3).

These estimated savings appear to assume a greater advantage for PET over other techniques than has been proved to be the case. Since PET is time-consuming and there are likely to be scheduling problems, the replacement of other tests in itself may not necessarily reduce the

time spent in coronary care. Comparison of sensitivity and specificity data for PET and thallium tests suggests that the introduction of PET would result in improved diagnosis for a relatively small number of patients. As noted previously, false positive diagnoses might be avoided for three to 50 patients in a patient population of 500. For these patients the time in coronary care might be shortened by one to two days. Cost savings would be in the region of $2000-75,000.

If PET were available, it is likely that it would replace thallium stress tests and possibly also exercise ECG. The level of savings through replacement of thallium stress tests would depend on the proportion of patients currently receiving these tests. If all the patient group referred to PET would have been subjected to the thallium stress test in the absence of PET, the saving would be in the region of $275,000. It is possible that not all patients referred to PET would have received the thallium test in its absence, and some patients may be subjected to both tests. A realistic range for the savings which could be achieved in this way would be $200,000-$275,000.

In the assessment of myocardial viability in patients with damaged hearts being considered for surgery, savings would be achieved if PET reduced the numbers of patients submitted to ineffective revascularisation. Whether in fact PET would have this effect would depend on current practices in the management of these patients. If decision-making on revascularisation currently relies on thallium redistribution scans, then replacement by PET could result in an increase in the number of cases identified as having viable myocardium and referred for surgery. In fact, the procedures used in decision-making on these patients are likely to vary from institution to institution.

If the use of PET results in an increase in the number of patients being referred for revascularisation, there could be savings to society through increased productivity and reduced dependence of the patients concerned, as well as the benefits of improved quality and possibly length of life. At this stage, however, it is not possible to draw any conclusions on the effects of this application of PET on health care and social costs.

If the use of PET results in some patients being referred to vascular surgery rather than to heart transplant, the savings would be considerable. Given the rigorous selection of patients for heart transplantation in Australia, the believed that very few patients if any, would be affected in this way. Currently about 80 patients a year undergo heart transplant in Australia. It seems most unlikely that more than one a year would be referred instead to vascular surgery as a result of a PET study. The saving for such a patient would be in the region of $100,000 (including post-transplant costs).

Applications in refractory epilepsy

It has been suggested that the use of PET in the pre-surgical assessment of patients with refractory epilepsy would result in cost

savings through reduction in the use of surface EEG monitoring, and replacement of intracranial EEG and SPECT (3).

Some reduction in the use of surface EEG and video monitoring might occur if PET results are seen as sufficiently reliable to reduce the number of surface EEG recordings of seizures needed for localisation of foci. Some reduction in video monitoring might also occur through the replacement of SPECT, but at present it is not used at every institution assessing refractory epilepsy patients for surgery. It is suggested that it is most unlikely that the reduction in the monitoring period would be more than an average of one week per patient. At a total throughput for two PET units of 250 refractory epilepsy patients a year, the total savings would not be expected to be more than $790,000. Replacement of the SPECT procedure itself at a cost of $320 per test might total $40,000.

A reduction in the use of intracranial EEG would be expected, but its magnitude is uncertain. The Panel estimated that the average cost per patient of intracranial EEG was $4,850. If the reduction in its use is in the range 20-40 per cent, the savings for 250 patients would be in the range $242,000-$485,000.

Brain tumour applications

In the management of cerebral glioma patients, it has been suggested that savings could be achieved through avoidance of brain biopsies, and reduction in the number of craniotomies (3). While PET may contribute to more efficient management of these patients and some reduction in procedures, it seems most unlikely that it will replace biopsies. It is extremely difficult to quantify the savings which could be achieved. If, say, 20-50 biopsies (with an approximate cost per procedure of $1,000) and 5-10 craniotomies (costing approximately $9,000 per procedure) are avoided annually, the savings could be in the region of $65,000-140,000 a year.

The introduction of PET would be unlikely to have a significant effect on outcome for these patients.

Summary

In summary, the introduction of PET could be expected to result in offsetting savings for health care which might be substantial, particularly in studies of refractory epilepsy patients, but it is most unlikely that they would approach the total costs of PET operation. For two PET units the total offsetting savings might be in the range $1.0-2.0M a year (30 per cent of total annual costs), but could conceivably be much less. An evaluation would be necessary to give a reliable indication of the magnitude of any savings for health care and society.

It is noted that in a 1990 study for the US Department of Health and Human Services it was estimated that increased usage of PET would increase Medicare costs in hospitals during the 1991 fiscal year by $US2.9-5.8M. PET was not identified as a technology that would have a cost-decreasing impact (52).

SAFETY ISSUES

The introduction of PET would raise safety issues in relation to the exposure of patients and staff to radiation, and the toxicity of radiopharmaceuticals administered to patients.

State governments are responsible for radiation safety aspects of medical equipment, usually through Radiation Committees. Advice to the Panel indicates that the radiation dose to a patient during an average PET study is well below the levels approved by the US FDA. However, in considering total radiation dose there is a need to take into account any additional studies performed, and the radiation dose from transmission scans performed for correction purposes. Nevertheless it would seem unlikely that radiation doses to patients would ever exceed approved limits.

Staff are exposed to radiation during the preparation of radiopharmaceuticals, their delivery and their injection into patients. Radiochemists involved in the preparation of radiopharmaceuticals are likely to be particularly affected and there would be a need to ensure that preparation facilities are adequately shielded. As would be normal in a nuclear medicine department, safety protocols would need to apply to all procedures. All staff should be supplied with dosimetry badges and records of radiation dosage should be maintained.

The Commonwealth Deparment of Community Services and Health is responsible for the approval of radiopharmaceuticals under the Therapeutic Goods Act. It seems likely that PET radiopharmaceuticals would be regarded as 'dispensed' for individual patients, and would not require approval. Each hospital would have a responsibility to see that quality control procedures are in place to ensure that these products are radiochemically pure, sterile and apyrogenic before administration to patients.

WORKFORCE IMPLICATIONS

As well as being a capital intensive technology, PET is labour intensive. While the impact of one or two PET units on employment opportunities would be very small, a proliferation of PET units could have a significant effect on the nuclear medicine and medical science workforce. There could be difficulties in finding personnel with the required expertise, particularly in radiochemistry and medical physics, and staff training requirements would be substantial. Such proliferation is, however, unlikely to occur in the short term.

Other effects on the health care workforce could be more significant in the short term. PET is often regarded as the 'premier' nuclear medicine technique and is the subject of a substantial proportion of the nuclear medicine literature. From the point of view of Australian nuclear medicine personnel the absence of PET in Australia means that they are out of touch with an important area of their own specialty. They would perceive the introduction of PET as contributing to staff development not only in the hospitals with the units but also in other

institutions, through cross referral of patients, collaborative projects, and exchanges of information in seminars and conferences. There could be a positive effect on staff morale, and a sense that Australian nuclear medicine had greater standing in the international community.

CONCLUSIONS AND RECOMMENDATIONS

Although PET can make a unique contribution to research and is efficacious in several specific clinical applications, the cost effectiveness of this high cost technology as a clinical tool is not yet clear. It is not considered that a sufficient case has been established to justify the routine use of PET as a clinical service in Australia.

If one or both PET facilities are established, all clinical usage should be incorporated in evaluation programs and regular reports on the programs should be provided to appropriate Commonwealth and State Government authorities and relevant professional bodies.

The use of PET as a reference technique to assist in the further development of alternative techniques would be desirable. At least initially, emphasis should be on development of SPECT techniques. Comparison with MRI in studies of refractory epilepsy patients may also be useful.

Ideally, the evaluation of the effects of PET on clinical decision making and patient outcome should include randomised controlled trials (RCTs). The difficulty of this approach in the assessment of diagnostic imaging technologies is noted, but it is suggested that RCTs might be feasible in assessing the role of PET in cardiac examinations, particularly in the assessment of myocardial viablity.

If one or both of the proposed PET facilities are established in Australia, it is recommended that

- the technology should be subject to a coordinated evaluation of clinical and cost benefits, involving both units;
- all patients scanned should be suitable for inclusion in evaluation protocols; criteria for the selection of patients for PET scans should be developed;
- evaluations undertaken should include assessment of patient benefit from the use of PET in cardiac and neurological applications, in comparison with alternatives, particularly SPECT in cardiac and glioma studies, and SPECT and MRI in epilepsy studies;
- studies should be prospective and closely involve referring clinicians. An independent organisation with expertise in evaluation should also be involved;

- regular reports on the evaluations should be sent to appropriate Commonwealth and State authorities and professional bodies; and

- no further units should be considered until the evaluations, including detailed cost benefit analysis, are completed.

APPENDIX 1: RADIOPHARMACEUTICALS USED IN PET

Table 6 lists the most commonly used radionuclides, with their half-lives. Table 7 lists the radiopharmaceuticals in which the radionuclides are most frequently incorporated, and the physiological function to which they are applied.

TABLE 6: POSITRON-EMITTING RADIONUCLIDES

Radionuclide	Half-life (approx) mins
carbon-11 (^{11}C)	20
nitrogen-13 (^{13}N)	10
oxygen-15 (^{15}O)	2.1
fluorine-18 (^{18}F)	110
bromine-75 (^{75}Br)	101
rubidium-82 (^{82}Ru)	1.25

Source: Council on Scientific Affairs, American Medical Association "Cyclotrons and radiopharmaceuticals in positron emission tomography". JAMA 1988;259:1854-1860.

TABLE 7: RADIOPHARMACEUTICALS USED IN PET

Radiopharmaceutical	Use
2-deoxy-2-(^{18}F)-fluoro-D-glucose (FDG)	glucose metabolism
1-(^{11}C)-2-deoxy-D-glucose	glucose metabolism
(^{18}F) fluoro-DOPA	dopamine metabolism
^{11}C and ^{18}F-labelled butyrophenones	dopamine receptors
^{15}O-oxygen	oxygen utilisation
^{15}O-water	blood flow
^{13}N-ammonia	blood volume
^{11}C-labelled fatty acids	oxidative metabolism
rubidium-82	myocardial blood flow

Source: (in part): Council on Scientific Affairs, American Medical Association "Cyclotrons and radiopharmaceuticals in positron emission tomography". JAMA 1988;259:1854-1860.

APPENDIX 2: TYPES OF PET INSTALLATION

A PET installation can have different levels of flexibility. For the widest range of studies to be possible, there must be a cyclotron on site, with facilities for manual production of 'tailor-made' tracers as well as automated production of those most commonly used. If automated production systems only are available, there is less scope for innovative studies, but the commonest types of PET studies can be carried out.

At the most basic level, there is no cyclotron on site and PET operation has to depend on generator produced radionuclides (rubidium-82 produced from strontium-82, or gallium-68 from germanium-68), or fluorine-18 labelled tracers supplied from a cyclotron elsewhere. The latter will be possible only if the cyclotron is close enough for the fluorine-18 to be delivered within four hours of production. As well as placing severe restrictions on the kinds of studies that could be undertaken, this type of operation could be hampered by uncertainties in the availability of the generator systems, and the logistic difficulties of transporting fluorine-18. There could be major scheduling problems for both producers and users of the fluorine-18.

It has been suggested that a PET unit in Melbourne could be operated with fluorine-18 supplied from the cyclotron at Royal Prince Alfred Hospital. This would involve a prolonged production process for the synthesis of fluorine-18, to obtain a highly active sample. The normal time required is 75 minutes with a further 70 minutes for the automated synthesis of FDG.

The sample of FDG would then be transported to Sydney Airport (20 minutes under normal conditions, 40 minutes at peak hour). The sample would need to arrive at the Airport 20 minutes before flight departure and flight time is 75 minutes if there are no delays (in fact there usually are delays of 10 to 30 minutes and sometimes longer). Unloading in Melbourne would require 15-20 minutes and transport to Austin Hospital would take 35-45 minutes. Delivery to the patient could be done in 10 minutes. Assuming no traffic delays the total time required from completion of synthesis of the fluorine-18 to delivery to the first patient would be four hours, and the sample would have lost half of its activity. If delays of the usual kind occur, the time required could be as high as five hours.

A possible time table is as follows

6.15am	commence preparation of fluorine-18
8.15am	commence synthesis of FDG
9.25am	depart for Sydney Airport
9.45am	arrive at Airport, arrange for loading on aircraft
10.00am	aircraft departs from Sydney

11.15am arrives Melbourne, sample unloaded

11.30am sample departs from Melbourne Airport

12.05pm arrives Austin Hospital

12.15pm sample delivered to patient.

By this time the activity of the sample will be less than 25 per cent of the original level. For the next patient, activity may be down to 15 per cent.

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