MEDICAL CYCLOTRON FACILITIES

a report by the

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ADVISORY

PANEL

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A report by the National Health Technology Advisory Panel on the desirability of a national medical cyclotron facility in Australia.

The Panel would welcome any comments or information relevant to the subject matter of this report. Correspondence should be directed to:

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THE NATIONAL HEALTH TECHNOLOGY ADVISORY PANEL

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- Dr R. Smith, Australian Atomic Energy Commission
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- Dr W. Burch, Royal Canberra Hospital
- Dr J. Deeble, Australian National University
- Australian and New Zealand Association of Physicians in Nuclear Medicine.
- Dr J. Bonnyman, Australian Radiation Laboratory

MEDICAL CYCLOTRON FACILITIES

CONTENTS

EXECUTIVE SUMMARY

- The National Health Technology Advisory Panel (NHTAP) has undertaken an examination of separate proposals from the Austin Hospital and the Australian Atomic Energy Commission for a medical cyclotron facility.

- The proponents have argued that a cyclotron facility would benefit Australia in areas of patient care, availability and export of radioisotopes, and medical research.

- The NHTAP considers that a cyclotron facility providing for radioisotope production and the diagnostic technique of positron emission tomography (PET) would have value for medical research.

- Such a facility could also improve or add to the investigational techniques available to health care.

  - Expansion of the range of radioisotopes available in Australia may improve the quality of some diagnostic procedures, particularly for thyroid conditions and pulmonary embolism.

  - As yet PET has very limited clinical application but has the potential to contribute to the management of a limited number of stroke and epilepsy patients. A further limitation of PET is the requirement that it be sited near a cyclotron.

- It is not clear that the marginal benefit to patient management and outcome would be sufficient to justify the cost of a medical cyclotron facility.

- More detailed study is required to assess the benefits of cyclotron radioisotope production and PET, taking into account the availability of other diagnostic technologies. In some cases benefit may be limited by lack of effective therapy.

- On the basis of evidence available to it, the Panel does not consider introduction of neutron beam therapy in Australia is justified at this stage.

- It is probable that a cyclotron facility would run at a loss and require on-going government support. Export opportunities may be limited because of vigorous competition from overseas suppliers. The Panel notes that commercial organisations are unwilling to establish cyclotron radioisotope production in Australia.

- Any increase in the domestic use of radioisotopes would result in additional costs to the health care system - the value of corresponding benefits is not certain.

- Estimates of cost in both proposals require detailed examination and appear to have underestimated expenditure in some areas.

- Considerably more work is needed to determine the potential gain to Australia from a national medical cyclotron facility and the true costs involved.

- The Panel recommends

  1) that a detailed technical and economic feasibility study should be undertaken to assess the cost effectiveness of establishing a medical cyclotron facility in Australia;

  2) that the value of medical research which would be made possible by a cyclotron should be considered by the National Health and Medical Research Council.

1. INTRODUCTION

A cyclotron is a machine designed to accelerate charged atomic particles to kinetic energies of many million electron volts (MeV). From an ion source in the centre of the device, charged particles are continuously accelerated by high frequency electrical fields while at the same time being constrained by a strong magnetic field to travel in an outward spiral path. The particle beam is finally deflected from the cyclotron at the point of maximum radius and guided along a vacuum tube with focussing and bending magnets to the target.

The major medical applications of the cyclotron are production of radioisotopes for nuclear medicine and the diagnostic technique of positron emission tomography (PET), and the use of particle beams for cancer therapy.

Proposals for an Australian Cyclotron

For a number of years there has been discussion in Australia of the possibility of establishing a cyclotron for medical applications, either as a stand-alone facility or in association with an institute for research in nuclear medicine. It has been argued that a cyclotron facility would result in clinical benefits by making possible the provision of diagnostic and therapeutic procedures presently unavailable in Australia, and the improvement of some existing procedures through the reduction of radiation dosage to patients and diagnostic staff and the application of superior techniques.

The cost of a medical cyclotron facility would however be high. At current prices the capital cost might be expected to be in the range $M6-10 with the annual operating costs of the order of $M1. Major benefits to Australian health care in terms of provision of routine diagnosis and therapy, and significant offsetting savings, would need to be demonstrated for these costs to be justified.

Earlier proposals envisaged establishment of a cyclotron at St George's Hospital, Sydney or at the premises of the Australian Atomic Energy Commission (AAEC) at Lucas Heights. A small cyclotron was used for research purposes at the Australian National University for several years until 1979. It had been shown to be capable of producing thallium-201, but was not ideal for radioisotope production, and was sold overseas.

Also in 1979, a working party including Department of Health representatives was set up by the Australian Institute of Nuclear Science and Engineering to consider the need for an Institute of Nuclear Radiation and Medicine. The Working Party recommended the establishment of an Institute, noting also that "the establishment of a cyclotron might need to be considered in the near future". In the event funds were not made

available for this project. A further proposal was put forward in May 1983 for a $25m national medical cyclotron facility at the University of Sydney, to be managed by the AAEC and to be associated with a national institute of nuclear medicine, but funds were not made available in the 1983/84 Budget for this project.

Late in 1983 the Commonwealth Government received two further proposals for a national institute of nuclear medicine incorporating a cyclotron facility. The Australian Atomic Energy Commission (AAEC) proposed the establishment of a facility in Sydney located at the Royal Prince Alfred Hospital. The Austin Hospital, Melbourne proposed an institute on its own premises, with a cyclotron facility which in addition to radioisotope production would provide for neutron beam therapy for cancer patients and positron emission tomography.

The Federal Minister for Health asked the National Health Technology Advisory Panel (NHTAP) to examine both proposals and report on the desirability of a national medical cyclotron facility as envisaged in each proposal. The central issue to be considered was whether such a facility would make a cost-effective contribution to Australian health care.

The NHTAP subsequently asked both organisations to supply more detailed information to assist in the assessment of the proposals. A detailed proposal for a multipurpose cyclotron facility was submitted by Austin Hospital in April 1984. In the meantime the AAEC prepared a revised submission for a cyclotron facility for radioisotope production only which was also made available to the NHTAP later that month. Both proposals had dropped the concept of an Institute.

The NHTAP has been given the task of both assessing the cost-effectiveness of a medical cyclotron and associated technologies and of commenting on two specific proposals. Because of time constraints associated with Ministerial discussions, it has not been possible to prepare a definitive report on these matters and a number of unresolved questions require further examination.

Medical Applications of Cyclotrons

Cyclotron-produced Radioisotopes

Radioisotopes are produced by directing the cyclotron beam at suitable targets. Unlike most of the isotopes produced in nuclear reactors, which possess excess neutrons and decay by ß-emission, many cyclotron-produced radioisotopes are neutron deficient and decay by electron capture or positron emission. They also tend to have shorter half-lives. Table I lists some cyclotron-produced radioisotopes which have been used in medical diagnosis, their half-lives and major applications.

The production of radioisotopes for diagnostic imaging procedures in nuclear medicine is the major commercial application of cyclotron technology. These products complement the reactor-produced radioisotopes available to nuclear medicine. Radioisotope imaging, whether using cyclotron or reactor-produced isotopes, has the potential to measure function as well as the anatomy of an organ. To obtain the image, the radioisotope is administered to the patient in the form of a suitable radiopharmaceutical, and the photon emissions (radioactivity) detected and visualized. As well as having a role in clinical diagnosis, radioisotope imaging is also used in medical research.

Positron Emission Tomography

The positron emitting radioisotopes produced at a cyclotron can be used in a new imaging modality known as positron emission tomography (PET). With positron emitters, high resolution may be achieved by the use of tomographic methods based on coincidence techniques. Interest in PET has been especially directed towards imaging of the brain.

Radioisotopes used in PET include carbon-11, oxygen-15 and nitrogen-13, whose stable isotopes form the principal body constituents. Consequently they have potential for application to a wide range of functional studies. As many of the useful positron-emitting radioisotopes have very short half lives, a PET system needs to be sited adjacent to a cyclotron.

Particle Beam Therapy

Therapies using various high energy particles have been tried in the management of cancer. Neutron beam therapy has been one of the most widely applied.

A neutron beam is produced by bombarding a suitable target such as beryllium with a charged particle beam from a cyclotron or other type of accelerator. The beam is then collimated directly on the tumour which is to be treated.

The use of proton beams and beams of heavier particles in cancer therapy require higher energy, more expensive cyclotrons than those currently proposed for Australia, and their impact on cancer management is uncertain. Consequently they are not further considered in this report.

Housing and Support Facilities

To protect the environment from radiation the cyclotron must be housed in a thickly-walled concrete building. As well as the cyclotron itself, high energy beam handling equipment is required in the main cell to direct beams to target areas. Radioisotope production requires cooled target equipment in shielded cells, cells for the processing of targets, laboratories for the preparation of radiopharmaceuticals and packaging and dispatch facilities.

Neutron beam therapy requires equipment in a shielded room adjacent to the main cell while PET equipment needs to be located in a room removed from the immediate area housing the cyclotron to avoid interference. If PET or neutron beam therapy is used at a cyclotron installation, patient handling facilities are also required. Finally, a workshop is required for the maintenance of the cyclotron and associated equipment.

Cyclotron Installations Overseas

Based principally on information supplied in the AAEC submission, and in a recent review of neutron beam therapy by an AAEC officer[1], Table II lists countries with medical cyclotrons and the number of currently installed cyclotrons, PET and neutron beam facilities in each country. Many of the facilities listed are not new, and installation dates range from 1955 to 1984.

About a third of the cyclotrons in the U.S.A. and a few of those in other countries are operated by private industry for the commercial production of medical radioisotopes. These installations would depend on the availability of large markets for commercial viability.

The data indicate that multipurpose installations with facilities for both PET and neutron beam therapy are not the norm. Most medical cyclotrons are used for radioisotope production only. About a third have associated PET facilities but relatively few are associated with neutron beam therapy.

2. CURRENT PROPOSALS FOR A MEDICAL CYCLOTRON FACILITY IN AUSTRALIA

AAEC Proposal

The AAEC proposes the establishment of a 40 MeV cyclotron facility at the Royal Prince Alfred Hospital, Sydney. The proposal is for a "production only" facility restricted to the production of radioisotopes. However, the NHTAP understands that the building proposed would permit later expansion to include additional facilities, and that the long term preference of the AAEC is for a multipurpose machine.

In its present form, the proposal envisages the production and distribution of short and medium half life radioisotopes for use in nuclear medicine, with processing and distribution being shared between the hospital site and the AAEC premises at Lucas Heights.

The Commission estimates the capital costs of the facility at $M10.0, annual operating costs (excluding capital charges) at $M0.65 and annual revenue from the sale of radioisotopes at $M1.15 (1983/84 values).

Austin Hospital Proposal

The Austin Hospital also proposes installation of a 40 MeV cyclotron, to be located in a new building in the hospital grounds.

In addition to production of radioisotopes for distribution throughout Australia and technetium-99m for Victoria, positron emitting isotopes would be generated for on-site PET. Distribution and marketing of radioisotopes could, if necessary, be undertaken in cooperation with another agency. The proposal also makes provision for neutron beam therapy facilities for treatment of cancer patients.

The hospital estimates capital costs at $M8.6, annual operating costs at $M1.3 and revenue from the sale of radioisotopes at $M1.0 (1983/84 values).

Estimated Costs of the Proposals

Table III compares the capital cost components for each proposal. Although the Austin Hospital estimate includes the substantial sums required for PET and neutron beam therapy, it is lower than the total envisaged by the AAEC, principally because of the much higher building cost in the AAEC estimate. The Panel understands that the building proposed by the AAEC allows for later expansion to include patient investigation and treatment modalities and research facilities. Plans for substantial additional capital expenditure at a later stage appear therefore to be implicit in the AAEC proposal. The AAEC

estimate also includes costs for extension of radioisotope processing facilities at Lucas Heights. The necessity for such an extension requires careful examination. The Austin Hospital proposal may have underestimated costs of radioisotope processing facilities.

The AAEC estimates for capital costs are understood to be based on advice obtained from various overseas sources. The corresponding Austin costings are based on information provided by a cyclotron manufacturer and an estimate provided by an Australian construction company (Costain).

In Table IV a comparison is given of estimated operating costs put forward in the proposals. As might be expected, operating costs are higher for the Austin Hospital proposal, owing to greater staffing requirements for the patient investigation and treatment components. However, the AAEC total does not include maintenance costs, and appears, therefore, to be an underestimate. It is also unclear as to whether full account has been taken in the AAEC submission of the costs of staff at Lucas Heights who would be associated with the facility. The Austin Hospital estimates appear not to have taken account of the higher cost involved in producing technetium-99m in a cyclotron rather than a reactor.

On the basis of an examination of the two estimates, the Panel considers that the capital cost of a 40 MeV cyclotron facility with provision for radioisotope production only, and with no provision for further expansion, might be in the region of $M6.0-7.0. The addition of PET would add $M1.6 to the cost, and neutron beam therapy a further $M1.5. The operating costs, excluding capital charges and depreciation, might be in the region of $M1.0-1.5 per annum. These figures are, however, intended only to give an indication of the magnitude of costs involved. A detailed financial analysis would be necessary to arrive at reliable figures.

3. CYCLOTRON-PRODUCED RADIOISOTOPES: APPLICATIONS AND BENEFITS

Apart from the short-lived radioisotopes used in PET, medically significant cyclotron radioisotopes include iodine-123, gallium-67, indium-111, and thallium-201. There is also increasing interest in the use of krypton-81m and gold-195m. Currently the longer-lived isotopes gallium-67, indium-111 and thallium-201 are imported into Australia, but the others are not available in this country.

The applications of each radioisotope and the potential benefits of Australian production are discussed below.

Iodine-123

Use in Thyroid Studies compared with current methods in Australia

Technically, iodine-123 is the most suitable radioisotope for use in thyroid imaging and uptake studies. The gamma energy of its photon emission (159 keV) is very suitable for use with gamma cameras, and owing to its short half-life (13 hours) and lack of significant particulate emission, it delivers a relatively low radiation dose to the thyroid. However, its short lifetime places limitations on its availability. For the grade of iodine-123 normally produced, the maximum acceptable time from production to use is about 24 hours. Long delivery times result in an increase in the proportions of the contaminants iodine-124 and iodine-125 relative to iodine-123 in the active component of the sample, negating some of the advantages of the radioisotope.[2] This problem could be reduced by the use of high purity iodine-123 which would enable an extension of the maximum acceptable time from production to use possibly allowing import into Australia. A new process for the production of high purity iodine-123 at a 40 MeV cyclotron has been developed in Canada but is not yet proven. It may also be produced at a higher energy cyclotron (70 MeV). The cost of importing high purity iodine - 123 would probably be substantial. In addition to high production and transport costs, loss of activity during transport would increase cost as a larger sample would be required.

The alternative radioisotopes for use in thyroid studies are principally technetium-99m and iodine-131. Table V gives figures for thyroid tests from an Australian Radiation Laboratory (ARL) survey of radiopharmaceuticals used in Australia in 1980 over a four week period. The figures indicate that 90% of thyroid radioisotope studies in Australia are performed with technetium-99m, 6% with iodine-131 and 4% with other radioisotopes.[3] The figures suggest that the total number of studies a year is in the region of 12,300.

Iodine-131 is suitable for thyroid radiotherapy but is less desirable for thyroid scans as it is a beta-emitter with a relatively long half-life (8 days) and delivers a high radiation dose to the thyroid. In addition the high gamma energy of its photon emission (364 keV) is poorly detected by gamma cameras.[2]

The reactor-produced isotope technetium-99m, like iodine-123, has a very suitable photon emission (140 keV) for gamma cameras and delivers a lower radiation dose to the thyroid than any iodine radioisotope. (Safety aspects related to use of iodine-123 are considered separately below.) The low uptake of technetium-99m by the thyroid is offset by the higher dose which is permitted by its favourable dosimetric characteristics. Technetium-99m has a half-life of 6 hours but delivery problems are overcome by its production at the site of utilization from molybdenum-99, a reactor-produced isotope with a half-life of 67 hours.[2] "Instant" technetium-99m may also be produced at a reactor or cyclotron.

A disadvantage of technetium-99m is that in a small number of cases, it leads to normal or increased uptakes by lesions which appear "cold" on radioiodide scans, leading to diagnostic problems. In a number of cases there is a need to repeat the scan with iodine-131. The ARL data[3] indicate that in Australia a total of about 750 patients a year are scanned with iodine-131. Thyroid scans are usually accompanied by quantitative uptake studies. In Australia these generally utilize technetium-99m.

Molybdenum generators used for technetium-99m production may be purchased from the AAEC. Overseas products are however highly competitive and a high proportion of the generators used in Australia are imported.

Further investigation is needed to establish the possibility of importing iodine-123 produced in high purity and the cost effectiveness of this option compared with local production. Further examination is also needed of the extent to which locally produced iodine-123 would be likely to replace technetium-99m for thyroid studies. While extensive replacement may be likely, relative costs and hospital budgetary considerations may impose some constraints.

Single Photon Emission Computed Tomography

Single photon emission computed tomography (SPECT), like PET, is a technique which can be used to produce a three dimensional map showing the planar distribution of a radiopharmaceutical within the body slice by slice. Unlike PET it uses more readily available single photon emitting radioisotopes such as technetium-99m, thallium-201, and xenon-133 as well as iodine-123, and does not require a site

adjacent to a cyclotron. It has been used to image cerebral blood flow, glucose metabolism, cerebro-spinal fluid circulation, and the lungs, heart and liver, and is already in use in Australia.

Iodine-123 is of particular interest in relation to the quantitative mapping of cerebral blood flow, previously possible only with PET, but which now can be performed with SPECT using isopropyl-iodoamphetamine-iodine-123 (IMP).[4] This technique has been applied to the localization of seizure foci in epileptic patients and the delineation of areas of cerebral ischaemia in patients with stroke. It may have a role similar to that proposed for PET (Section 3) in the management of epilepsy and reversible stroke, and could permit extension of the management procedures to sites away from a cyclotron. However to obtain good images, this technique requires expensive, highly sensitive detecting systems, conventional gamma camera systems being inadequate.[5]

Although IMP is the most promising agent for cerebral blood flow measurements with SPECT, other agents have been used, particularly the reactor-produced gas, xenon-133. This is a cheaper and more practical agent to use, but gives slightly poorer resolution.[5]

Renal Studies

Radioiodine-labelled hippurate has been used in the evaluation of kidney function to measure plasma flow. Iodine-123 is preferable to iodine-131 owing to its lower radiation hazard. Radioiodine-labelled hippurate does not appear to be used to any significant extent in Australia.

Labelling of monoclonal antibodies with Iodine 123 is referred to separately below.

Currently Imported Isotopes: Gallium-67, Thallium-201 and Indium-111

Gallium in the form of gallium citrate has a marked tendency to concentrate in tumours and inflammatory lesions, a property utilized in the detection of some forms of cancer and abscesses by nuclear imaging with gallium-67. The Austin Hospital submission estimates that 4500 doses a year of gallium-67 are used in Australia.

Thallium-201 is used in non-invasive myocardial imaging, taking advantage of the preferential uptake of the thallium by oxygenated heart muscle. According to Austin Hospital 6000 doses a year are used in Australia.

Indium-111 is currently used only experimentally in Australia with 200 doses imported annually but has significant potential for use in the radiolabelling of monoclonal antibodies.

According to the AAEC submission the current arrangements for the supply of the radioisotopes are unreliable and ineffective. The ARL has advised, however, that it is unaware of any significant supply problems with these isotopes.[6] Foreign exchange savings resulting from the replacement of imports would be offset by the initial capital and recurrent costs of the cyclotron and the need to purchase targets and spare parts from overseas. Further study is needed to assess trends in the use of these radioisotopes and their contribution to patient management and outcome.

Krypton-81m

Krypton-81m is a radioisotope with a very short half-life (13 seconds) produced in a generator system from the cyclotron-produced isotope rubidium-81 whose short half-life (4.7 hours) does not permit importation. The AAEC submission has pointed out the desirability of using krypton-81m in Australia in the diagnosis of pulmonary embolism.

Pulmonary embolism is a major cause of hospitalized patient death. Its diagnosis is clinically difficult and depends largely on nuclear medicine, particularly the V/Q scan. This technique involves a ventilation scan using a radioactive gas, a perfusion scan using a technetium-99m radiopharmaceutical, and a comparison of the two for a mismatch. Xenon-133 is commonly used for the ventilation scan but has the disadvantages that its long half-life and ß-emission result in a radiation hazard, and its radiation characteristics are not optimal for resolution by a gamma-camera. Krypton-81m is free of these disadvantages but availability problems limit its use to relatively few centres overseas. An alternative approach is to use a technetium-99m aerosol. In the past these aerosols have not been entirely satisfactory. A new microaerosol recently developed in Australia may offer significant improvement, but has yet to be proven.[7]

The Panel considers that further assessment is needed to determine the need for krypton-81m in Australia, in the light of results to be obtained from current trials of the technetium-99m microaerosol. Consideration should also be given to non-nuclear medicine procedures. A new ultrasound procedure for the diagnosis of pulmonary embolism has given promising results to date.[8] It is possible that this technique could represent an alternative to the V/Q scan if larger trials now in progress confirm the initial results, although it would be several years before it would be accepted as reliable. A preliminary study has indicated that nuclear magnetic resonance imaging may be applicable to the diagnosis of pulmonary embolism.[9]

Gold-195m

Gold-195m is produced in a generator from the cyclotron-produced radioisotope mercury-195m. It is used in the study of heart dynamics and has the advantage that its very short half-life (30 seconds) permits repeat scans free of background. At this stage this radioisotope is a research tool and its impact on health care would be small.

Labelling of Monoclonal antibodies

Development of monoclonal antibody (MCA) technology is of major significance to diagnosis and therapy and applications will continue to widen. Some diagnostic applications of MCAs require the labelling of the antibody with a suitable radioisotope to permit visualisation or location of the target antigen within the body (e.g. tumour antigen). Cyclotron-produced isotopes are of interest in this context, because of advantages provided in detection of emitted radiation or in reduced radiation burden to the patient.

Iodine-123 is one of several radioisotopes used to label monoclonal and polyclonal antibodies in research on the visualization of tumours. Its usefulness in this application is limited by its short half-life, the ease with which monoclonal antibodies are dehalogenated in vivo, and the fact that it cannot be used with technetium-99m for background subtraction because of overlapping photon energies. The latter problem could be partly overcome by tomographic techniques. Dehalogenation appears to present particular difficulties as a proportion of iodine from a labelled MCA will be removed and redistributed to the thyroid and other areas of the body.

Indium-111 is regarded as having a major use in future in the labelling of MCAs, attachment to the antibody through a suitable chelate being rapid and stable.

A note of caution needs to be sounded on diagnostic imaging with monoclonal antibodies. Several studies have been disappointing and a number of factors can contribute to poor results.[10] Moreover, the technique may have limited clinical relevance. Fairweather, Bradwell and Dykes have argued that accurate localization of tumours is only important in health care if local therapy is contemplated. They comment that it seems unlikely that antibody scanning can have a major impact on the management of the common malignant tumours unless more effective therapy can be devised, although it may be a useful research tool.[10]

The Panel feels that some of the claims for the use of radiolabelled MCAs in diagnostic imaging need to be assessed critically.

Revenue from the Sale of Radioisotopes

The AAEC and Austin Hospital proposals base their estimates of revenue from the sale of cyclotron-produced radioisotopes on the following assumptions:

AAEC

- 100% replacement of imported gallium-67, thallium-201 and indium-111;
- 100% replacement of isotopes used currently in thyroid scans by iodine-123;
- an assumed market for krypton-81m estimated on the basis of usage in the U.S.A.

Austin Hospital

- 100% replacement of imported gallium-67, thallium-201 and indium-111;
- 80% replacement of the technetium-99m and 100% replacement of the iodine-131 currently used in thyroid scans by iodine-123;
- supply of 40% of the Victorian market for technetium-99m.

Both estimates may be optimistic in their assumption of 100% replacement of imported gallium-67, indium-111 and thallium-201 as there would be vigorous competition from overseas suppliers. Overseas competition has been very significant in the case of reactor-produced radioisotopes. The AAEC has had difficulty in maintaining a satisfactory market share for these radioisotopes, and imported products account for a high proportion of the Australian market. Moreover it is generally believed that the industry overseas has overestimated markets for gallium-67 and thallium-201 and there is excess production capacity for cyclotron radioisotopes at present.[6]

The projected market figures might also be optimistic in respect of iodine-123. A survey of US practice in thyroid studies in 1981[11] showed that technetium-99m was used in 54% of all thyroid scans; iodine-131 accounted for 9% of thyroid scans and 54% of uptake studies; and iodine-123 was used in 35% of thyroid scans and 46% of uptake studies. The most common reasons given for not using iodine-123 were cost and availability problems. However, it is understood that with improved availability, the percentage use of iodine-123 is likely to have increased since 1981.

The AAEC suggests that in addition to revenue from Australian sales, an export market could be established. Further study would be needed to assess the size of this market. Again there must be some doubt as to how effectively an Australian facility could compete with overseas cyclotron facilities, particularly in a situation of excess capacity.

The Panel feels it is significant that commercial organisations are not prepared to establish a cyclotron for production purposes in this country because they believe it would be a loss-making enterprise. If cyclotron isotope production is to incur a loss which would be borne by Government, there is a need to determine whether the marginal benefit to health care would justify such expenditure.

Overall place of cylotron-produced radioisotope usage in diagnostic medicine

In assessing the impact an Australian cyclotron would have on health care, it would be highly desirable to get some sort of quantitative measure of its marginal benefit for health services. This measure would relate to the effect that usage of cyclotron-produced radioisotopes would have on overall patient management/outcome, taking into account the extent to which competing diagnostic modalities could more suitably be applied and the availability of effective therapy for the diagnosed conditions. This is no easy task. In discussions with the Panel, the proponents of the two cyclotron proposals have argued strongly for the desirability of readier access to certain radioisotopes to improve diagnostic medicine in Australia and increase patient safety. However, data relating to overall effect on patient care have not been forthcoming.

Support for cyclotron-related diagnostic technologies seems less strong in this country outside departments of nuclear medicine, and the suggestion has been made that radiological techniques based for example on nuclear magnetic resonance may provide more attractive, non-invasive, alternatives in some instances. Opinion appears to be polarised within the medical profession and the Panel feels that both unqualified enthusiasm for use of cyclotron produced radioisotopes and total avoidance of these products are unwarranted. A balanced viewpoint has been hard to obtain. The Panel considers that full consideration of benefits, disadvantages and costs of diagnostic radioisotope usage need to be clearly identified before a final decision is taken.

In discussion with representatives from the Austin Hospital and the AAEC, the major justification often put forward for improved availability of cyclotron-produced radioisotopes has been the benefit to medical research, rather than routine diagnosis. As with any diagnostic method, radioisotope-based procedures cannot realise their full

potential as patients will not necessarily present themselves for examination at a suitably early stage. Further, some of the conditions detected will not be manageable/curable or may be more readily diagnosed in other ways.

It is of interest that an earlier comparison of CT and radiodiagnostic methods for diagnosis of brain conditions demonstrated that CT scanning was superior to radioisotope imaging at all levels of diagnostic information.[12] There have been improvements in both areas since that study, and a new assessment would be of value.

Safety considerations

In general the Panel recognizes the desirability of reducing radiation dosages used in diagnostic techniques. The use of iodine-123 would result in a reduced radiation dose in the small percentage of thyroid studies currently performed with iodine-131, while the use of krypton-81m would reduce the radiation dose in lung scans. For the most part, however, cyclotron-produced radioisotopes would not significantly affect radiation dosage to patients and in some cases may actually increase it.

Appendix B of the AAEC submission gives a tabulation of the monetary benefit which would arise from the use of iodine-123 in thyroid scans in Australia. The ARL has advised that for several reasons the calculation is invalid.[6]

In the first place the ICRP model used in the calculation applies only to populations which have normal age and sex distributions and life expectancy. The monetary value (∝) assigned to the unit of effective radiation exposure has not been shown to apply to thyroid patients. The population considered by the AAEC includes 39% hyperthyroids many of whom would subsequently receive iodine-131 radiotherapy as part of their treatment. In these cases it would be inappropriate to consider the reduced radiation dose in the diagnostic treatment to have any beneficial effect.

Even more importantly, the calculation is based on the assumption that all thyroid scans are performed with iodine-131 when in fact in 90% of cases iodine-123 would replace technetium-99m, and would give a slight increase in radiation dose. In addition, the AAEC has assumed that the patient dose for iodine-123 would be 100 microcuries, but it has been reported that in the USA the average patient dose is about 200 microcuries.[11]

The assumption in the AAEC calculation that if iodine-123 were available it would be used for 100% of thyroid scans in Australia is also open to question although it is recognised that there would be widespread usage of this isotope.

In summary, the use of iodine-123 in thyroid studies would result in improved diagnostic accuracy and reduced radiation dose for perhaps 700-1000 patients a year. For many of these, however, the reduction in radiation dose would have no value, as they would in any case be subjected to radiation therapy with iodine-131. The Panel does not consider that a monetary value can be reliably assigned to the benefits of using iodine-123, but any such figure would be many times smaller than that estimated by the AAEC.

There is also a need to put radiation hazards to patients in perspective. Standard X-ray procedures also result in significant levels of radiation to patients. Magnetic resonance imaging techniques may in future offer advantages over use of radioisotopes or X-rays from the point of view of patient safety.

4. POSITRON EMISSION TOMOGRAPHY

Principles and Applications

Positron emission tomography (PET) was introduced into clinical research in 1975. Unlike CT scanning which identifies structures, PET is concerned with functional imaging, and has allowed the quantitative mapping of cerebral blood flow, blood volume, glucose and oxygen utilisation, protein synthesis and receptor-ligand binding.

When a positron is emitted from the nucleus of an atom it travels only a short distance before combining with a free electron. In this event the two particles are annihilated and two photons produced which move away from the point of annihilation in precisely opposite directions. By placing two detectors on opposite sides of a positron emitting source both photons can be detected simultaneously and it is possible to define a line upon which the positron source must lie. By recording many thousands of these annihilation events and using tomographic computing technology, images can be built up.

In addition to studies of normal brain function, PET has been applied to studies of cerebrovascular disorders, degenerative brain disorders, schizophrenia, epilepsy, and tumours. While most effort has concentrated on the brain, other parts of the body have also been studied, particularly the heart and the liver.

Recent Results of PET Studies

Cerebral blood flow and oxygen utilization studies are usually undertaken with oxygen-15 as the positron emitter, in the form of oxygen gas (for oxygen utilization) or carbon dioxide for blood flow measurements. Cerebral blood volume measurements are undertaken with carbon-11 labelled carbon monoxide while glucose metabolism is usually studied with fluorine-18 labelled fluorodeoxyglucose although carbon-11 labelled glucose has also been used.

PET measurements of cerebral blood flow, oxygen utilization and glucose metabolism have been used to determine the extent of functional impairment resulting from cerebrovascular conditions such as stroke, and have been reported to give a more accurate definition of the extent of impairment than CT scans.[13,14] PET examinations can also demonstrate the presence of viable cerebral tissue whose function is impaired by an ischaemic situation but where cell damage is not yet permanent. These examinations can show whether or not by-pass surgery is indicated.[15]

In studies of epileptics, PET scans with fluorodeoxyglucose have detected hypometabolic brain zones considered most likely to be responsible for seizures. The technique gives some false results but a combination with electrophysiological techniques is believed to give more reliable information than either method alone. The combination has been used in presurgical evaluation to determine the site of resection.[13]

PET scans using fluorodeoxyglucose appear to be much more sensitive than CT scans for detecting localized regions of brain dysfunction in patients with dementia. The PET scans give distinctly different patterns for Alzheimer's disease, multiple infarct dementia and depression. PET may ultimately have a role in the earlier diagnosis of Alzheimer's disease,[13] although the value of this diagnosis would be limited in the absence of effective therapy. Studies of cerebral blood flow and oxygen metabolism in schizophrenics have provided support for the hypothesis that an abnormality in hemisphere laterality may underline schizophrenic illness.[16] PET studies of a type of cerebral tumour have indicated that there is a correlation between the degree of tumour malignancy and rate of glucose uptake.[15]

There is some controversy over the validity of results from PET glucose metabolism studies using fluorodeoxyglucose. Glucose metabolism in the brain is complex and rapid. Use of the deoxyglucose analogue is based on the assumption that its metabolism proceeds part of the way along the glucose metabolic path, and stops when deoxyglucose-6-phosphate is formed. Some results indicate, however, that this compound is much less stable in the brain than was believed, so that results of PET studies based on the assumption of its stability would be incorrect. These findings are disputed by the researchers working with PET. It has been suggested that "PET has become a virtual industry with a momentum of its own" and that any problems associated with the technique are unlikely to be satisfactorily analysed.[17] This controversy does not apply to PET studies which are not based on use of fluorodeoxyglucose.

Another problem in PET investigations arises from fluctuations which can occur in normal brain metabolism and which can be mistaken for abnormalities. For example if ears are blocked and eyes closed there is a relative decrease in right-sided metabolism. The need to control ambient test conditions has been pointed out.[13]

In summary PET investigations overseas are providing interesting results which may lead to improved understanding of a number of disorders, as well as normal brain function, and to new diagnostic approaches. To date, however, the effect of PET on clinical practice is extremely limited and t must be regarded at this stage as primarily a research tool. Questions on the validity of some PET techniques need to be resolved.

Effect on Australian Health Care

In general the Panel considers that since PET is largely a research tool, its direct effect on Australian health care would be relatively minor. Austin Hospital has suggested, however, that it could find clinical application in the management of stroke and intractable epilepsy.

In the case of intractable epilepsy the hospital argues that PET could significantly shorten the period required to assess patients for surgery (currently 3 months). This application would affect about 80 patients a year at the national epilepsy referral centre at the Austin Hospital, reducing waiting times and the pressure for creation of another treatment centre, with resulting cost savings. The Panel sees some merit in this argument but considers that further research may be required to establish a routine clinical procedure. As noted previously the validity of the fluorodeoxyglucose scanning technique used in epilepsy studies has been questioned. The Panel considers that there should be a detailed examination of the suggestion by the Austin Hospital to establish whether PET scanning would in fact shorten the assessment period, to estimate cost savings, and to identify benefits to patients.

In the case of stroke PET could be used to identify patients with potentially reversible lesions. The Austin Hospital has suggested that availability of PET would permit improved assessment of stroke victims for possible therapy. The Panel accepts that PET could play a useful role in this area provided that effective means of therapy were available. The Panel believes that at least initially the work in this area would be in the category of research. If it were successful the benefits would be significant, and the Panel considers this proposal should be examined in more detail. Such examination should include consideration of whether findings from PET investigations could be used to develop other diagnostic techniques which would allow the therapeutic procedure to be applied in hospitals without PET facilities.

Austin Hospital has also suggested the application of PET to studies of patients with schizophrenia, dementia, tumours, and movement disorders, and to drug distribution studies. While such studies could make a useful contribution to the international research effort, the Panel considers that they would be unlikely to affect Australian health care in the short to medium term.

5. NEUTRON BEAM THERAPY

Applications and Overseas Results

Interest in neutron beams for cancer therapy arose a number of years ago from laboratory work which indicated an advantage for neutron beams over conventional photon radiation in that neutron beams have a lower oxygen enhancement effect (an improved ability to destroy hypoxic cells).

The hypoxic region in a tumour lies between the anoxic core and the well oxygenated (euoxic) outer regions. The resistance to radiation of hypoxic regions compared to euoxic regions can result in the regrowth of tumours as the destruction of the euoxic region permits increased availability of oxygen to the surviving hypoxic cells. The oxygen enhancement ratio (OER) is the ratio of the dose required to kill hypoxic cells to that required to kill normally oxygenated cells. For photon radiation the OER is 2.5-3.0 while for neutrons in the range 10-60 MeV it is 1.6-1.7.

Another potential advantage of neutron beam therapy is that it results in reduced repair capability in irradiated malignant cells. These advantages are, however, offset by problems with current technology including poor penetration of tissue by the beam and wide penumbras, difficulties in dose measurement, fixed field sizes and positions, and production of radioactivity in equipment and tissue. These problems enhance the likelihood of complications.

Clinical trials of neutron beam therapy for various types of cancer have been undertaken in Europe, the U.S.A. and Japan. Cancers treated have included tumours of the head, neck and brain, lung carcinomas, soft tissue sarcomas, bone tumours, and tumours of the pelvic region. A frequent pattern in reports of this work is that encouraging results from one institution cannot be confirmed at others.

The first randomized trials comparing neutron beam with photon radiation were commenced at Hammersmith Hospital, England in 1971. The very encouraging results obtained with head and neck tumours were not confirmed by randomized trials combining patients in Scotland, F.R.G. and Holland.[18]

Similar trials in the U.S.A. comparing neutrons only, mixed-beam and conventional radiation for the treatment of head and neck cancer did not give statistically significant differences in local control rates, complication rates or median survival rates with the three modalities.[19,20] However a U.S.A. study on the treatment of metastatic neck nodes has indicated a statistically significant advantage for a mixed beam protocol.[21] Good local control of tumours of the

salivary glands was obtained in England, Holland and the U.S.A., with survival rates depending on the type of cancer, but the U.S.A. results suggest that results with photon irradiation are not significantly worse.[18]

In the treatment of brain tumours the Hammersmith group found that neutron beam irradiation resulted in local control but severe complications and workers in Scotland and Holland found no benefit in the use of neutrons rather than photons.[18] Similar results were obtained in the U.S.A.[19] and Japan.[22]

Good results were obtained in England in the neutron beam therapy of soft tissue sarcomas but results elsewhere have varied widely and with a significant proportion of severe complications.[18] Encouraging results on primary bone tumours in the F.R.G. were not observed in Holland,[18] but a combination of neutron beam therapy and chemotherapy in the treatment of osteosarcoma has given promising results in Japan.[22]

Results from the F.R.G. on the treatment of bronchial carcinoma indicate no significant advantage for neutron beam therapy over conventional treatment, although elsewhere more favourable results have been reported.[18,22] Limited studies on neutron beam treatment of Pancoast's tumour of the lung have given encouraging results.[18,22]

Varying results have been obtained in Europe, the U.S.A. and Japan in the treatment of tumours of the pelvic region. Preliminary results from the U.S.A. of mixed beam therapy of urinary bladder carcinomas were encouraging[19] but a randomized trial in Manchester comparing neutron and photon therapy for this condition did not show a significant difference between the two groups.[18] A Dutch study comparing neutrons and photons for the treatment of advanced tumours of the bladder and rectum showed that there was neglible gain in the use of neutrons.[23] In the treatment of carcinoma of the cervix results reported from European work do not indicate any advantage for neutron beam therapy[18] while the results of Japanese work indicate a lower rate of local recurrence with neutron therapy but a higher rate of complications.[22]

At this time assessments of neutron beam therapy by overseas workers tend to take the view that more work is needed to establish whether it has a useful role. Catterall considers that advantages have been shown for neutron beam therapy and that problems are caused by use of inferior machines.[24] The Edinburgh group, however, has concluded that as yet there is no real evidence that neutron therapy affords an enhanced therapeutic ratio compared to photon therapy in the treatment of most common forms of cancer, and further clinical trials with higher energy cyclotrons are needed.[25]

In a review of European experience in neutron beam therapy, Wambersie has noted[18] that most centres have failed to demonstrate a definite advantage of neutron therapy compared to high energy photon therapy for most tumour sites and/or tumour types. He considers that a key problem is to identify tumours suitable for neutron therapy.[18]

Effect on Australian Health Care

The Austin Hospital submission has identified persons with tumours of the rectum, head, neck, brain and bladder as candidates for neutron beam therapy in Australia and has estimated that there would be a total of 1,500 patients per year with these conditions. Overseas work has not, however, demonstrated that neutron beam therapy has any advantage over conventional treatment for tumours of the brain and rectum. Results for tumours of the head and neck and bladder are conflicting and a case for neutron beam treatment cannot be considered to have been established.

It is possible that new equipment in the U.S. and Europe with better depth dosing properties will give more favourable results for neutron beam therapy. On the basis of the evidence to date, however, the Panel is of the opinion that there would be minimal benefit to Australian health care from the introduction of neutron beam therapy, and the additional capital cost of over $1.5 million which would be involved in providing for this modality at a cyclotron facility cannot be justified.

6. OPTIONS FOR MEDICAL CYCLOTRON FACILITIES IN AUSTRALIA

The Panel notes that the cyclotron facilities proposed by Austin Hospital and the AAEC are not necessarily the only options available. The Panel has identified the following options as worthy of further examination.

- No cyclotron facility in Australia

  This option would provide significant savings in capital and recurrent expenditure. The non-availability of a cyclotron would probably have, at most, only a small effect on the health care of Australians generally, given the current availability of imported cyclotron-produced isotopes and other diagnostic methods. There would be disadvantages to medical research including the delay in developing expertise in some areas of nuclear medicine.

- A 40 MeV cyclotron facility for radioisotope production only (AAEC proposal)

  An expanded range of cyclotron-produced isotopes would be available to workers in Australia, but sales would depend on the success in meeting competition from imported products. Availability of iodine-123 would encourage medical research and provide some improvement in diagnostic techniques for thyroid conditions. Exclusion of PET would result in capital savings of about $1.6 million, reduced operating costs, and disadvantage to medical research.

  Representatives of both the Austin Hospital and AAEC have suggested to the Panel that a cyclotron should be in close proximity to a hospital. If a production-only facility is envisaged, it is not clear why this should be the case. In the AAEC proposal this philosophy has led to the difficulty of a production facility which would be split between two sites. The Panel sees significant value in a hospital site only if additional functions for the cyclotron are envisaged.

- A small cyclotron for PET only

  A 16 MeV cyclotron for PET only would reduce capital costs by about $3.9 million. Even smaller cyclotrons may be available for PET, allowing further reduction of costs. This option would provide a localised research facility with some potential to contribute to management of a limited group of patients, but would not provide a national source for radioisotopes.

- A 40 MeV cyclotron facility incorporating a PET system (Austin Hospital proposal with neutron beam therapy excluded)

  This option would require a hospital site and would combine a national production facility with a dedicated research unit, which would have the potential for some routine clinical diagnosis.

- A 40 MeV cyclotron for radioisotope production only and a small cyclotron for PET at a different site

  This option would be more expensive but would give increased flexibility. Only the small cyclotron would need to be located at a hospital.

7. CONCLUSIONS AND RECOMMENDATIONS

The Panel sees merit in both the AAEC and Austin Hospital proposals and considers that while there is no case at present for the introduction of neutron beam therapy, cyclotron radioisotope production and PET could benefit medical research in Australia. The value of a cyclotron to medical research has been stressed by representatives of both the Austin Hospital and the AAEC. The Panel considers it is possible that research applications might represent the main justification for an Australian cyclotron and that the value of such a facility to medical research deserves further consideration.

In the area of clinical application benefit would be limited primarily to improvements in diagnostic procedures through the use of iodine-123 and krypton-81m, and possibly improved management of a limited number of stroke and epilepsy patients through the use of PET.

The Panel is not yet convinced, however, that the benefits to health care from a medical cyclotron facility are sufficient to warrant the substantial cost involved. A number of issues need to be examined in more detail before a clear answer to this question can be given. These include:

- expected capital and operating costs;
- likely size of domestic and export markets for cyclotron-produced radioisotopes, taking into account competition from overseas suppliers and the existence of excess capacity overseas;
- economic impact on health care of previously unavailable radioisotopes, including added cost to health services, any cost savings, and comparison with possible alternatives;
- overall place of cyclotron-produced radioisotope methods in medical diagnosis, taking account of non-nuclear medicine techniques and the expected effects of these methods on patient management and outcome;
- contribution of PET to patient benefit and cost savings in the management of stroke and epilepsy patients, including the question of whether effective therapy is available which can utilize PET results;
- contribution of cyclotron-produced radioisotopes and PET to Australian medical research, including the possibility of contributing to the development of new products and procedures with commercial potential;

- practicability of combining in a single facility the commercial function of radioisotope production with the primarily research function of PET, and the feasibility of separate cyclotron facilities for radioisotope production and PET respectively;
- further appraisal of safety considerations;
- assessment of optimal siting and management arrangements, including management of radiopharmaceutical processing and distribution.

The Panel recommends

1) that a detailed technical and economic feasibility study of both the Austin Hospital and AAEC proposals should be undertaken to address these issues and to provide a comparative cost-benefit analysis of the options identified in Section 6 of this report.

2) that the value of medical research which would be made possible by a cyclotron facility should be considered by the NH & MRC.

Consultancy services should be utilized, particularly for the financial, economic and marketing aspects of the study. Efforts should be made to draw on overseas experience to aid in the assessment, as required.

TABLE I: SOME CYCLOTRON-PRODUCED RADIOISOTOPES USED IN NUCLEAR MEDICINE

Radioisotope	Half-life (t 1/2)	Principal Radiation (MeV)	Applications
carbon-11 (^{11}C)	20.3 mins	β^+ γ= 0.51	PET: Cerebral blood volume, pH, glucose metabolism, cardiac shunts, lung function
nitrogen-13 (^{13}N)	10.0 mins	β^+ γ= 0.51	PET: cerebral tumours, lung function
oxygen-15 (^{15}O)	2.1 mins	β^+ γ= 0.51	PET: cerebral blood flow, oxygen utilization
fluorine-18 (^{18}F)	110 mins	β^+ γ= 0.51	PET: cerebral glucose metabolism
potassium-43 (^{43}K)	22.4 hrs	β^- γ= 0.37-.62	Multiple electrolyte studies
iron-52 (^{52}Fe)	8.2 hrs	β^+ γ= 0.16-0.51	Bone marrow
gallium-67 (^{67}Ga)	78 hrs	γ= 0.18-0.30	Soft tissue tumours and abscesses
krypton-81m (^{81m}Kr)	13 secs	γ= 0.19	Lung function, cerebral perfusion
rubidium-81 (^{81}Rb)	4.7 hrs	β^+ γ= various	Red cell destruction, generation of ^{81m}Kr
indium-111 (^{111}In)	2.8 days	γ= 0.17-0.25	Monoclonal antibodies, abscess detection, tumour detection, platelet function
iodine-123 (^{123}I)	13 hrs	γ= 0.16	Thyroid function, renal function, cerebral blood flow
thallium-201 (^{201}Tl)	74 hrs	γ= 0.17	Myocardial function

TABLE II: COUNTRIES WITH CYCLOTRONS USED FOR MEDICAL PURPOSES*

Country	No of Cyclotrons[1] of 40 MeV or More	No of Smaller[1] Cyclotrons	No of PET Facilities[1]	No of Neutron Beam Facilities[2]
Belgium	3	2	2	1
Brazil	-	1	-	-
Canada	1	-	1	-
Czechoslovakia		1	-	-
Finland	-	3	-	-
France	2	3	2	1
FRG	2	5	4	1, 2[3]
GDR	-	1	-	1, 1[3]
India	1	-	-	-
Italy	2	1	-	-
Japan	3	5	3	2
ROK	1	-	1	-
Netherlands	1	3	1	1[3]
Poland[4]	-	1	-	1
Saudia Arabia	-	1	1	1
S. Africa	-	1	-	-
Sweden	1	3	2	-
Switzerland	2	-	1	-
U.K.	4	3	2	2, 1[3]
U.S.A.	10	21	9	4, 2[3]
USSR	-	1	-	-
Yugoslavia	-	1	-	-
TOTAL	33	56	29	14, 9[3]

* Planned installations are not included.

1. Source: AAEC submission "The Case for a National Medical Cyclotron" except where otherwise indicated.

2. Source: Allen, J.B., "Neutron Therapy" Australasian Radiol. 1983 27:195-214.

3. Neutron beam derived from a source other than a cyclotron.

4. Source: Shoyszewski et al, Int. J. Radiat. Oncol. Biol. Phys. 1982 Oct; 8(10):1781-6.

TABLE III: COMPARISON OF CAPITAL COST COMPONENTS OF THE TWO PROPOSALS

Component	Austin Hospital ($ million)	AAEC ($ million)
Building	2.4	6.4
Cyclotron	2.5	2.5
Target system	0.05	
Hot cells	0.06	0.6 (six)
Neutron beam therapy	1.7	-
PET	1.6	-
Processing and distribution of radiopharmaceticals	0.2	0.5
TOTAL	8.6	10.0

TABLE IV: COMPARISON OF RECURRENT COSTS
(EXCLUDING CAPITAL CHARGES AND DEPRECIATION)

Component	Austin Hospital $000	AAEC $000
Staff		328
- technical support, radiopharm production, distribution	296	
- therapy	61	
- administrative	117	
- ancilliary	31	
Targets/materials for radiopharm production	228	250
Distribution of radiopharm	50	?
Maintenance		
- equipment	368	?
- building	35	?
Medical consumables	15	-
Administrative costs	15	?
Power and services	123	70
TOTAL	1 339	648

TABLE V: THYROID STUDIES IN AUSTRALIA OVER FOUR WEEKS IN 1980

Radioisotope Used	No of Tests
iodine-131	56
technetium-99m	855
caesium-131	32
iodine-125	6
TOTAL	949

Source: D.W. Keam, "Patient Absorbed Dose and Radiation Risk in Nuclear Medicine", paper given at the Annual Scientific Meeting of the Australian and New Zealand Society of Nuclear Medicine, Perth, May 1983.

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