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THE CASE FOR A NATIONAL MEDICAL CYCLOTRON FACILITY

Presented by

R. SMITH

on behalf of the
Australian Atomic Energy Commission

Paper for presentation at the
Australian Medical Cyclotron Workshop
Canberra, 11 December 1984

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THE CASE FOR A NATIONAL MEDICAL CYCLOTRON FACILITY

1. INTRODUCTION

The title has been changed from "A Case for a medical cyclotron in Australia" (quoted in the program) to "The case for a national medical cyclotron facility" to emphasise the national features of the case being put forward by the Australian AEC with the support of the Royal Prince Alfred Hospital.

Since cyclotrons and the associated equipment are complex and costly, it is unrealistic to expect that the Federal Government will fund more than one facility at the present time. Thus it appears obvious that this facility should be designed and used to achieve maximum national benefit.

In this context the AAEC proposition is to install a dual-purpose cyclotron with two national purposes:

(1) the production of cyclotron radioisotopes for distribution to nuclear medicine centres throughout Australia and the near geographic region for diagnoses of a wide variety of medical conditions; and

(2) the provision, in association with the cyclotron, of a national nuclear medicine/PET centre for research and training as well as the evaluation of clinical benefits - with nation-wide access of clinical researchers guaranteed through a co-operative user arrangement [along the lines of the Australian Institute of Nuclear Science and Engineering (AINSE)]. At this centre, a facility would be installed for positron emission tomography (PET), using positron-emitting radioisotopes from the cyclotron.

The first purpose takes priority with the second being a cost-effective addition to achieve optimal and fair use of such a costly

national facility.

To achieve these optimal and equitable national benefits it is clear that implementation at the Federal level, particularly in regard to the second purpose, requires joint action between the Portfolios of Health, and Resources and Energy; the former because the ultimate objective is improved health care; and the latter because it embraces the AAEC which already has the responsibility, expertise, and established infrastructure for the production and distribution of radioisotopes, together with a clear mandate to apply nuclear science and technology for medical purposes.

The AAEC welcomes the opportunity at this workshop to discuss the proposition with medical specialists and representatives of Health Authorities to try to achieve a common national view.

In a total cost-benefit sense we believe the conclusions that must be reached are that a national medical cyclotron facility along the lines above is justified; that it should be implemented by joint action between the Department of Health and the AAEC; and that to make most effective use of existing facilities and expertise and to achieve optimal benefit it should be owned and operated by the AAEC and be located in Sydney at a major teaching hospital.

Here we are not saying that a case does not exist for PET facilities (with or without a cyclotron) in other centres in Australia. However these are seen as serving specialist and regional interests and they do not have the priority which is reserved to a first facility serving broader national purposes. At a national level the primary aim of PET studies **at this time** (to paraphrase Jones[1]) should not be to carry out clinical diagnoses on a few selected patients, but rather to obtain new scientific information on human disease and its treatment which can be transferred to and used by the practising medical community both within the country and throughout the world.

2. NUCLEAR MEDICINE IN AUSTRALIA

Nuclear medicine facilities exist in some 50 hospitals throughout Australia, using radioisotopes as biological tracers for non-invasive early diagnosis of functional disorders - currently in some 150,000 patients annually. Diagnostic nuclear medicine relies on the fact that almost any element can be made radioactive (in a nuclear reactor or a cyclotron). That element, or a biologically active compound containing it, is thereby labelled at the atomic level and, when incorporated in the human body, can be located, traced and quantitatively measured to provide an intimate view of the machinery of the body in action. Radioactively-labelled pharmaceuticals are usually designed to participate in metabolic processes of particular organs or tissues, where they can be detected, visualised and the data subjected to computer analysis.

The unique power of nuclear medicine relies on using radioactive atoms as tracers to follow dynamic biochemical and physiological processes and to provide evidence of normal or abnormal function. In principle it can follow events at the molecular level but this sensitivity is limited in practice by the capability of instruments to detect each radioactive disintegration and locate it in space and time . A further constraint is the problem of labelling biological molecules or substances with appropriate radioactive atoms to study specific organ functions.

Nuclear medicine procedures using labelled compounds provide precise data about organ function and pathological deviations. This functional data allows diagnosis to be made at the earliest stages of disease before any anatomical changes are discernible and when the effects may be reversed, thereby enhancing the possibility of a cure. At the present time it appears most unlikely that alternative techniques will replace the biological tracer principle in nuclear medicine for functional studies; the other diagnostic modalities are seen to have a complementary role. Techniques such as computerised tomography (CT) and nuclear magnetic resonance imaging (NMR) can provide precise anatomical information but they do not give the functional and dynamic data obtainable from the nuclear technique.

Nuclear medicine in Australia grew to maturity in the 1970s as a result of the availability of short-lived radioisotopes (particularly technetium-99m) from the AAEC's research reactor HIFAR and the development of a nationwide distribution service provided by the AAEC's Isotope Division. In the year ending March 1984, the Commission supplied radioisotope products to the value of $2.2 million (28,000 shipments); of this total more than $1.7 million came from medical applications.

Today nuclear medicine in Australia is a well established medical speciality which is accepted as an important and integral part of the overall health care system particularly in major referral hospitals. This is recognised in the government schedule of fees under medical benefits for a wide range of investigations. Fees are paid not only for the investigation but also for the supply of the radioisotope.

However, despite the sophistication in training and clinical resources available to the Australian physician in nuclear medicine, the range of the service that can be provided today is significantly below that of most other developed countries. This is because of the absence of an Australian cyclotron and a guaranteed access to cyclotron-produced isotopes for specific diagnoses.

Although reactor-produced technetium-99m is regarded as an ideal radioisotope in nuclear medicine, it lacks certain properties which, in turn, impose constraints on the scope of its applications. For example:

- its half life of 6 hours is too long for certain applications where repeat studies are required over a short period of time.

- despite the success radiopharmacists have had in formulating preparations of ^{99m}Tc which concentrate in individual organs and tissues, the range of Tc-compounds available is limited and for certain important fields of investigation the appropriate technetium agent has yet to be discovered. Examples of these are a Tc-agent which will uptake in primary malignancies or inflammatory processes

and a Tc-agent which will discriminate between the viable and non-viable myocardium.

- other fields exist where, for a variety of reasons, the use of a Tc-agent provides imperfect diagnostic information. Examples of this occur in thyroid studies where ^{99m}Tc is taken up by the gland but cannot be organified into thyroid hormone and in ^{99m}Tc-labelled biological macromolecules.

Hence for a variety of reasons the goals of nuclear medicine cannot be achieved through the exclusive use of ^{99m}Tc. Other radioactive tracers are required; of those which have the required physical, chemical and biological properties, most are neutron-deficient radioisotopes obtainable only with a cyclotron.

Radioisotopes for use in nuclear medicine should be short-lived, preferably with a half-life that matches the time required for diagnosis as this results in minimal radiation exposure to the patient. Because of Australia's geographical isolation, and the times involved for import from overseas, the requirement for short-lived radioisotopes cannot be satisfied in Australia unless there is a domestic production capability. In the case of reactor-produced radioisotopes the national need can be satisfied by the Australian AEC's reactor HIFAR. But no domestic capability exists for cyclotron-produced radioisotopes. This means that none of the short-lived cyclotron products (half-lives of less than one day) are available in Australia and the import of gallium-67, thallium-201 and indium-111 which have half-lives of about 3 days is continually at risk from international air transport dislocations.

A good example of a cyclotron product that is not available is iodine-123, which is accepted internationally as the agent of choice for the diagnosis of thyroid disorders. Because its half-life is 13 hours, it cannot be imported with any prospect of reliability. The alternative for the Australian physician in nuclear medicine to achieve effective diagnosis is the reactor-produced iodine-131 (half life of 8 days) which results in high radiation exposure to the patient; alternatively technetium-99m is

used but this has an unacceptable high incidence of false negatives.

Australia is also disadvantaged in that it does not have available the recently developed technique of PET for more precise investigation of organ function; this technique requires positron-emitting isotopes which can only be produced effectively with a cyclotron. An important constraint with PET is that many of the radioisotopes of interest are of such a short half-life that the studies using them can only be carried out close to the site of the cyclotron.

3. CYCLOTRONS FOR NUCLEAR MEDICINE

In nuclear reactors, radioisotopes are produced by bombarding target elements with neutrons to produce unstable nuclei with an excess of neutrons. Other radioisotopes can be produced by bombarding targets with a high energy beam of charged particles such as protons or deuterons; this is usually performed in a cyclotron or other type of accelerator. In this case, the radioisotopes have unstable, neutron-deficient nuclei which decay by emitting radiation in somewhat different modes from the reactor-produced radioisotopes, and some of these modes aid their detection in nuclear medicine.

A cyclotron is a device for producing high energy beams of charged particles. From an ion source in the centre, charged particles are continuously accelerated by high frequency electric fields while they are constrained by a strong magnetic field to travel in an outward spiral path in an evacuated gap between two cylindrically-shaped magnetic poles. The spiral path of the particle beam increases in radius with increase in energy until the beam is finally deflected from the cyclotron at the point of maximum radius. The extracted particle beam is guided along a vacuum tube with focusing and bending magnets, called the beam transport system, to the point where the high energy particles can be used to bombard targets to produce radioisotopes. Modern cyclotrons are designed to produce beams, almost automatically, over a wide range of energies for a variety of

charged particles. Because high levels of radiation are produced during operation, the cyclotron is contained in a vault with thick concrete walls (at least 2.2 metres for 40 MeV operation).

Figure 1 shows the growth in the number of cyclotrons in medical use over the last thirty-five years, both those used for general medical purposes and those dedicated to commercial radioisotope production. The geographical location of medical cyclotrons throughout the world is illustrated in Figure 2. Figure 1 shows that there are some 90 cyclotrons in use for medical applications and that the number has increased dramatically in recent years.

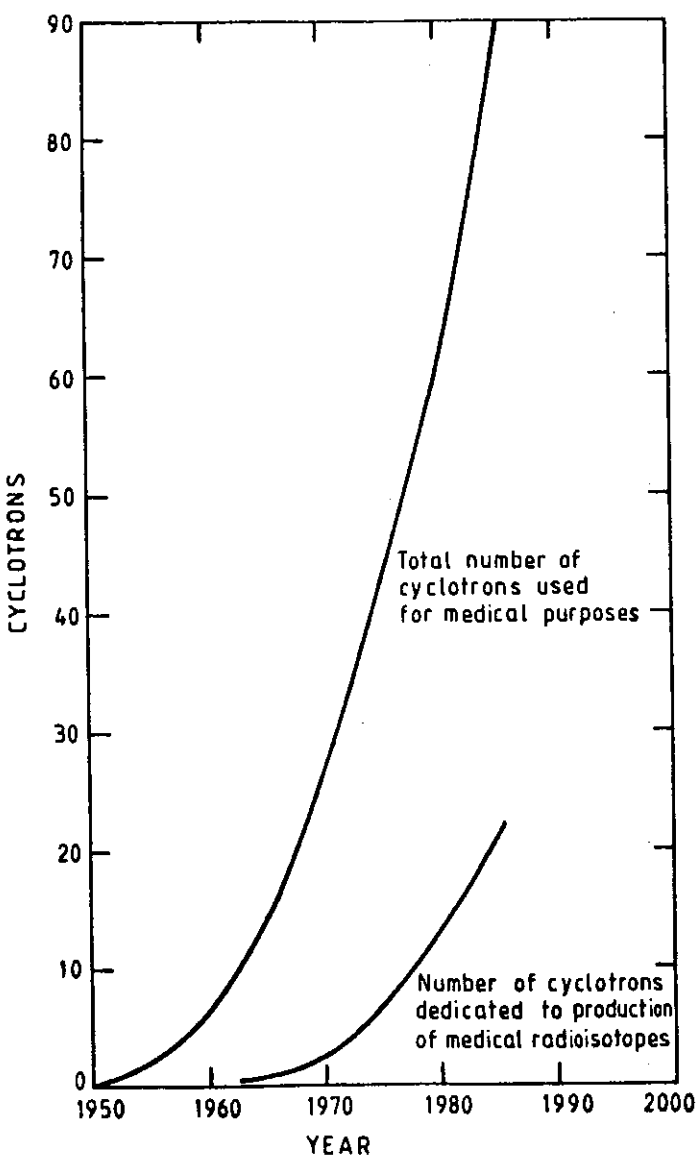


Figure 1 GROWTH IN NUMBER OF CYCLOTRONS FOR MEDICAL PURPOSES

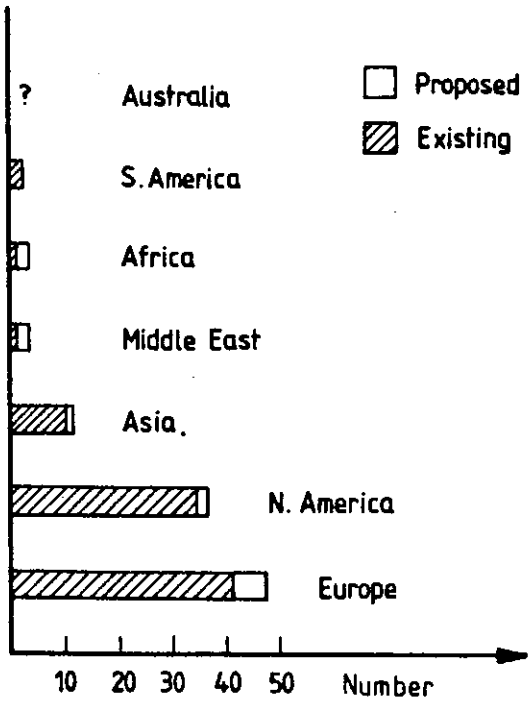


Figure 2. Cyclotron Installations Used for Medical Purposes (By region, excluding the U.S.S.R.)

Recently-installed cyclotrons fall into four broad categories:

(a) Commercial radioisotope production cyclotrons

These have been installed, usually by private industry, to satisfy the commercial demand for cyclotron radioisotopes in nuclear medicine. In total there will be 21 installations by 1985 (e.g. UK-2, France-1, Belgium-1, Japan-3, USA-13) owned mainly by companies such as Mallinckrodt, New England Nuclear, Medi-physics, and Amersham International. Such cyclotrons aim to operate continuously in a production mode to achieve competitive costs.

(b) Cyclotrons primarily for supporting PET studies

About 45 PET centres have been or are being established (e.g. Belgium-3, France-2, Germany-5, Japan-3, UK-2, USA-15) to take advantage of the newly developed high resolution imaging technique of positron emission tomography (PET) for **in-vivo** studies of basic physiological processes. The

technique requires positron-emitting radioisotopes produced by a cyclotron. Radioisotopes of particular interest are, carbon-11, nitrogen-13, oxygen-15 and fluorine-18, which have very short half-lives of 20, 10, 2 and 110 minutes respectively; with the exception of ^{18}F, PET studies using these radioisotopes can only be carried out close to the site of the cyclotron.

(c) Cyclotrons for cancer therapy

Considerable interest has developed in recent years in the use of neutron beams for cancer therapy as they are claimed to be more effective than other forms of radiation therapy for some types of cancer (mainly because they are considered to be more effective against hypoxic cells in bulky tumours). Cyclotrons such as those at the Clatterbridge Hospital, Liverpool, UK: The M.D. Anderson Tumour Institute, Houston, USA: The University of Washington, Seattle, USA: and The Veterans' Administration Hospital, UCLA, USA, have been installed primarily for this purpose. The neutron beams are produced by bombardment of a beryllium target with the proton beam from the cyclotron. A multicentre clinical trial is currently underway in the USA on this controversial subject.

(d) Multipurpose facilities

These may be used for several of the purposes above as well as for general research studies in radiation biology and activation analysis.

The AAEC Proposal

The AAEC proposal is for a dual-purpose cyclotron facility to serve the purposes in categories (a) and (b) above, viz., to produce radioisotopes for distribution to nuclear medicine centres throughout Australia and the near region on a quasi-commercial basis and to use the remainder of the time for PET studies. This takes into account that the demand for cyclotron radioisotopes which need to be produced and distributed in the commercial production mode can be satisfied with less than 8 hours machine time per day and thus adequate time is available for

PET studies (see figure 3). The use of the cyclotron beams for neutron therapy is not included in the proposal as it is not considered to be justified at the present time; however, the option would be available, particularly for research purposes, albeit at a significant increase in cost.

4. MEDICAL APPLICATIONS OF CYCLOTRON-PRODUCED RADIOISOTOPES

Table 1 lists the common cyclotron-produced radioisotopes currently being used in nuclear medicine, together with the half-life ($T_{\frac{1}{2}}$), and the energy of the emitted radiation (E γ keV).

These can be classified into two categories:

(i) Those which are photon emitters and can be used with existing* nuclear medicine equipment

(* Existing equipment includes Single Photon Emission Computed Tomography (SPECT) cameras.)

These would be available to all nuclear medicine centres throughout Australia and in the near geographic region through a production and distribution service akin to that provided already by the AAEC for reactor-produced radioisotopes. The application and benefits of having these radioisotopes available in Australia have been described by Quinlan[2] in an earlier paper at this workshop. A summary of the medical applications of this group of radioisotopes is given in Table 2.

The properties of interest to the physician in nuclear medicine for general use in hospitals are:

- short half-life to reduce the radiation dose to the patient and staff;

- suitable radiation to permit effective detection and collimation (usually photons in the energy range 100-250 keV);

- a chemistry which allows the radioisotope to be incorporated in chemical compounds capable of participating in biological processes of interest.

At present the most favoured cyclotron-produced radioisotopes for general use are: gallium-67, iodine-123, indium-111, thallium-201, krypton-81m and gold-195m.

(ii) Those which are positron emitters and require PET instrumentation

These, depending on their half-life, can be further sub-divided into those that can only be used at the site of the cyclotron and those which could be used at a site distant from the cyclotron.

The medical applications and benefits of having these radioisotopes available in Australia are described in following papers at this Workshop by Potchen[3] and Doyle.[4] In summary the applications are outlined in Table 3.

5. TECHNICAL FACILITIES

The Cyclotron

The basic technical requirement is a variable energy cyclotron capable of producing a range of medical radioisotopes in quantities sufficient to satisfy the Australian demand, with some residual capacity to meet prospective exports. This requirement can be satisfied by a commercially available medium energy 40 MeV machine. The decision on the size of machine to choose is influenced by a number of factors:

(i) The cost of the cyclotron installation increases roughly proportionally with the maximum energy required.

TABLE 1

PRINCIPAL CYCLOTRON RADIOISOTOPES OF MEDICAL INTEREST

(A) Photon emitting radioisotopes suitable for use in existing nuclear medicine equipment:

	($T_{\frac{1}{2}}$)	E(keV)
Iodine 123	13.0h	159
Indium 111	67.2h	172,245
Thallium 201	73.5h	70,167
Gallium 67	78.3h	93,185,300
Krypton 81m	13.3s	191
(Rubidium 81 generator	4.58h)	
Gold 195m	30.6s	262
(Mercury 195m generator	40.0h)	

(B) Positron emitting radioisotopes requiring PET instrumentation:

Fluorine 18	109.7m	511
Gallium 68	68.3m	511
(Germanium 68 generator	287d)	
Rubidium 82	76s	511
(Strontium 82 generator	25d)	
Oxygen 15	2.03m	511
Nitrogen 13	9.96m	511
Carbon 11	20.3m	511

TABLE 2

PRINCIPAL CLINICAL APPLICATIONS OF PHOTON EMITTING CYCLOTRON RADIOISOTOPES SUITABLE FOR USE WITH STANDARD NUCLEAR MEDICINE EQUIPMENT

Iodine 123		
iodide	-	assessment of thyroid function and diagnosis of thyroid disease.
iodo amphetamine	-	measurement of cerebral blood flow and identification of viable tissue.
fatty acids	-	measurement of myocardial metabolism.
monoclonal antibodies	-	cancer detection and monitoring of tumour progress.
hippurate	-	assessment of renal function.
fibrinogen	-	detection of thrombi.
Indium 111		
monoclonal antibodies	-	detection of cancer and monitoring of tumour progress.
platelets	-	detection of thrombi.
white cells	-	abscess, investigation of inflammation.
DTPA	-	assessment of renal function, CSF shunt.
Thallium 201		
chloride	-	assessment of myocardial perfusion and tissue viability, parathyroid tumour.
Gallium 67		
citrate	-	detection of abscess, active inflammation and cancer.
Krypton 81m (Rubidium 81 generator)		
inert gas	-	pulmonary ventilation, cardiac function.
Gold 195m (Mercury 195m generator)		
cyanide	-	cardiac function, blood flow.

TABLE 3

PRINCIPAL APPLICATIONS OF POSITRON-EMITTING CYCLOTRON RADIOISOTOPES

(A) Positron emitting radioisotopes requiring PET instrumentation not necessarily at the site of the cyclotron.

Fluorine 18	
deoxyglucose	- glucose metabolism in central nervous system and cardio vascular system, investigation of epilepsy, stroke, dementia, ischaemia, psychiatric disorders, Huntington's chorea and Alzheimer's disease.
methane	- cerebral blood flow.
receptor agents	- assessment of neuroreceptor pharmacology.
Gallium 68	
monoclonal antibodies	- detection of cancer and monitoring of tumour progress.
EDTA	- cerebral blood volume.
Rubidium 82 (Strontium 82 generator)	
potassium analogue	- blood flow, cardiac function and myocardial viability.

(B) Positron emitting radioisotopes requiring PET instrumentation close to the site of production.

Oxygen 15*	
oxygen	- oxygen metabolism, oxygen utilisation, tissue viability.
water, carbon dioxide	- blood flow.
carbon monoxide	- blood volume.
Nitrogen 13*	
ammonia	- tissue perfusion and metabolic function.
amino acids	- metabolism and permeability.
nitrous oxide	- measurement of blood flow.
BCNU	- assessment of tumour drug levels.
Carbon 11*	
deoxyglucose, free fatty acids and amino acids	- investigation of various metabolites.
carbon monoxide	- blood volume.
carbon dioxide	- tissue pH and blood flow.
receptor agents	- assessment of receptor and transmitter pharmacology.
methyl glucose	- glucose transport.
leucine, methionine	- protein synthesis

* These short lived radioisotopes can be incorporated in a wide variety of molecules in order to investigate metabolism, blood flow, perfusion, tissue pH, transport and protein synthesis. They can also be incorporated in compounds of pharmacological interest. Their role to date has been in clinical research with extensive areas of application; stroke, psychiatric disorders, myocardial viability, pulmonary metabolism, neuro-physiological stimulation studies, monitoring of pharmaco-kinetics.

(ii) Very short-lived radioisotopes such as ^{11}C, ^{13}N, and ^{15}O required primarily for PET scanning and basic research require a particle energy of only 7-15 MeV. However, they can also be produced conveniently on a medium energy machine.

(iii) Radioisotopes such as ^{18}F, ^{75}Br, ^{81}Rb, ^{67}Ga, ^{111}In, and ^{201}Tl, all of which are widely used in nuclear medicine and other research, require a particle energy in the range 20-40 MeV which can be provided by a medium-energy medium-cost cyclotron.

(iv) ^{123}I, which is strongly recommended for diagnostic nuclear medicine of the thyroid, some other organs and for clinical research, can be prepared at two levels of purity. Until very recently the high purity form has required an energy of at least 60 MeV and preferably 70 MeV for optimum production. This form has optimum imaging properties and yields minimum radiation dose to the patient. In Europe, two major suppliers provide the high purity form which is more widely used in that area. The nuclear reaction leading to the low purity form requires only an energy of 24 MeV, which represents considerable savings in capital and operating costs, and thus the unit cost is about half that of the high purity form. However, its imaging properties are inferior and it yields a higher radiation exposure to the patient, the more so the longer the time between production and administration to the patient.

A recent development has been made known to the AAEC by Atomic Energy of Canada Ltd (AECL) which claims to have developed a new process for producing high-purity ^{123}I, requiring an energy of only 25 MeV. The claim appears to be well substantiated and AECL is expected to offer the process to the AAEC. If the costs and product quality are acceptable, there is no need for a 60-70 MeV machine to satisfy the strong demand on the part of Australian physicians in nuclear medicine for pure ^{123}I.

(v) A limited capability for neutron radiation therapy would be available from a machine with a maximum energy of 40 MeV, and a

considerably increased capability would be available from a machine with a 70 MeV maximum energy, with a small additional capability for proton radiation therapy. Present evidence for the benefits from increased capability for neutron therapy is controversial and there is little justification for a high energy machine for this application at the present time.

(vi) Recent purchases of cyclotrons have been mainly machines in the medium energy range and manufacturers have developed considerable experience in optimising their performance.

TABLE 4
CYCLOTRONS COMMERCIALLY AVAILABLE FOR MEDICAL PURPOSES

Manufacturer	Model	Particle and Energy (MeV)				External Beam Current (μA)
		p	d	^{3}He	^{4}He	
Scanditronix,	MC-16F	17	15	13	17	30-50
Uppsala,	MC-28F	28	14	21	28	30-65
Sweden	MC-35	8-35	4-18	10-47	8-35	30-65
	MC-40	10-40	5-20	13-53	10-40	30-65
	MC-50	13-50	7-25	17-66	13-50	30-50
	MC-60	15-60	8-30	20-78	15-60	30-50
The Cyclotron *	CS-22PD	20	11	-	-	60-100
Corporation,	CV-28	2-24	4-14	6-36	8-28	40-100
Berkeley, USA	CV-45(a)	12-45	7-24	-	-	50-200
	CP-60(a)	15-60	-	-	-	200
Japan Steel	BC168	16	8	-	-	50
Works, Tokyo	BC1710	17	10	-	-	50
CGR-MeV, Buc,	325	16	8	-	-	50
France	520	3-24	3-15	7-31	10-30	50-100
	560	5-40	10-20	15-52	20-40	50-100
	930	10-80	10-50	20-130	20-100	30-40

(a) Negative ion p = proton d = deuteron

* Now Computer Technology and Imaging Inc. which may be offering a somewhat different range of machines.

There are four manufacturers of cyclotrons suitable for medical purposes - sufficient to ensure competitive tenders. These are listed in Table 4 with the various models offered. Each manufacturer sells a variety of machines; some have variable energy, whereas others have fixed energy; some accelerate positive ions whereas others accelerate negative ions; some can accelerate only one particle whereas others are multiparticle machines. The basic costs of similar cyclotrons from each manufacturer are very similar.

The PET Scanner

Commercial PET scanners have broadly developed from the initial work of Terpergossian at St Louis, Phelps at UCLA and Eriksen in Sweden. While in the early years of development many University centres built their own scanners, this is not now considered to be worthwhile. Today the commercial scanners have reached a high degree of sophistication and performance (resolution less than 5 mm) and the appropriate course for Australia is to purchase such a machine.

A number of variations on the basic design are available from at least six manufacturers. The actual specification of the machine - whether head or whole body, the number of slices, the resolution, sensitivity, etc - need further discussion with prospective users. The cost is a function primarily of the number of detectors which in turn depends on the number of image planes - which may be up to 15. A PET scanner suited to Australian needs could be expected to fall in the range of $1.5 - 3.0 million.

Major Ancillary Facilities

For commercial production the major ancillary facilities are:

- Beam-handling equipment in the main cyclotron vault to direct beams to target areas (including magnets and computer).

- Shielded and cooled target equipment in shielded cells possibly with a pneumatic tube facility for rapid transportation of products to

laboratories.

- Radionuclide processing laboratory at the cyclotron site for preparation of targets, remote processing of irradiated targets in shielded cells and some processing of radioisotopes.

- Extensions to radiochemical processing laboratories at Lucas Heights where the longer lived radioisotopes would receive final processing into radiopharmaceuticals for nationwide distribution and where benefit would be gained from infrastructure already in existence for radiopharmaceutical production, quality control, marketing and distribution.

- Electrical and mechanical maintenance workshop.

- Limited packaging and dispatch facilities at the cyclotron site.

- Accommodation for the operating and maintenance staff.

For the PET centre additional target systems and hot cells will be required to produce the range of labelled biological compounds and additional accommodation facilities are required to house the research workers and allow for handling of patients.

6. MODE OF OPERATION

Figure 3 shows a notional operating schedule which allows for:

- the production of PET radioisotopes during the day-time on 5 days each week,

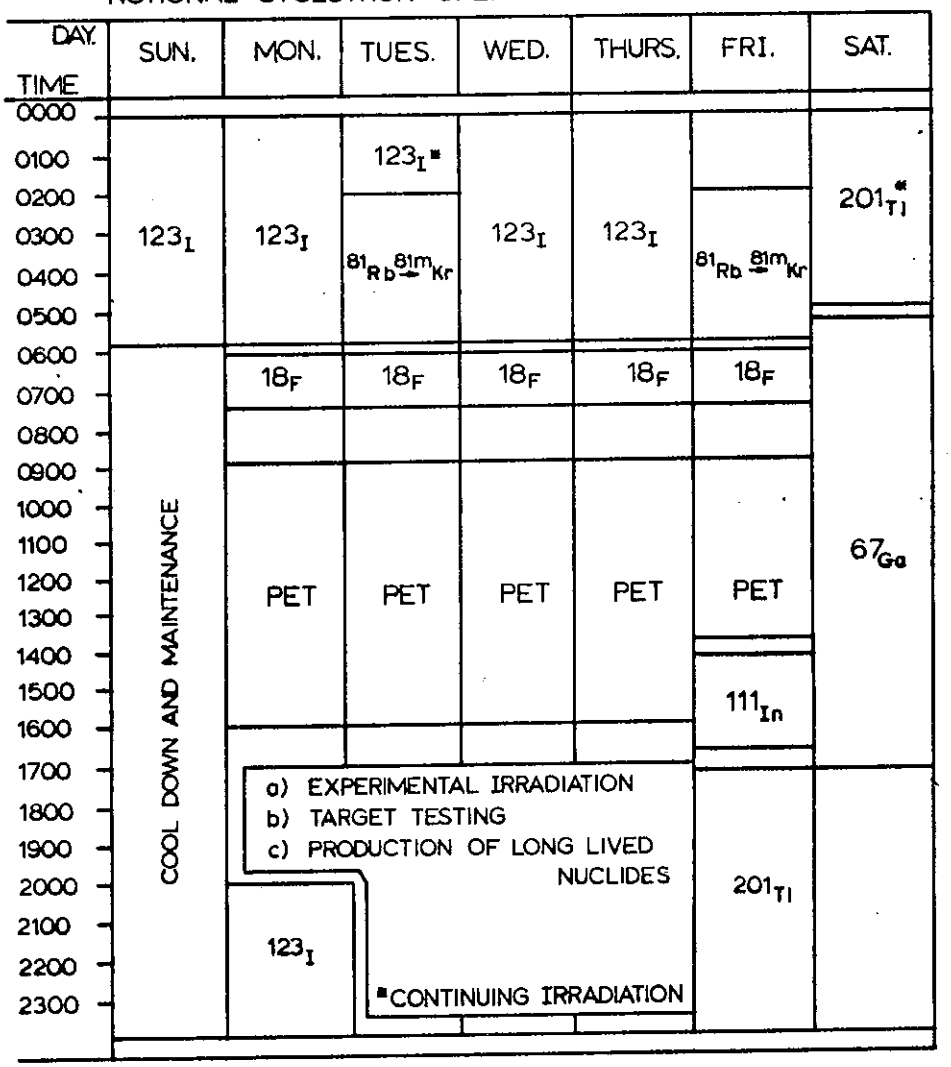
- the daily production of ^{123}I,

- the daily production of ^{18}F

- the twice weekly production of ^{81}Rb

FIGURE 3.

NOTIONAL CYCLOTRON OPERATING SCHEDULE



. the once weekly production of ^{201}Tl, ^{67}Ga and ^{111}In

This demonstrates the feasibility of dual purpose operation of the cyclotron - for PET studies in the daytime and for commercial production in the evening and night shifts.

7. COSTS

Capital Costs

Preliminary budget estimates of building and equipment costs at 1984 prices are given below, based on information provided by cyclotron manufacturers and the operators of cyclotron installations in North America and Europe. It is assumed that:

(a) The cyclotron will be located at Royal Prince Alfred Hospital, Sydney, and hot cell facilities for primary processing of the target material will be located adjacent to the cyclotron.

(b) No funding is required for the land on which the installation is sited.

(c) The final processing, dispensing, quality control, packaging and dispatch will be done at Lucas Heights using, with some augmentation, the existing infrastructure for commercial production of radioisotopes.

BUDGET CAPITAL COST ESTIMATES

Production Facility	$Million
At RPA Hospital	
Variable energy 40 MeV cyclotron	2.5
Building - including the cyclotron vault and space for service facilities, laboratories, hot cells and staff.	6.4
Shielded Processing cells (6 off)	0.6
At Lucas Heights	
Extension to processing building	0.375
Fume cupboards, and processing and dispensing cells and glove boxes	0.125
TOTAL	10.00
Nuclear Medicine/PET Centre Facility	
PET facility	1.5-3.0
Accommodation for patient handling) Accommodation for research staff)	0.2
Equipment for automatic radiochemical processing	0.5
TOTAL	2.2-3.7

Operating Budget

(A) Commercial Production

The estimated annual operating cost of the cyclotron and the associated radioisotope processing facilities is expected to be more than offset by revenue from the sale of cyclotron products based on the following considerations.

The annual operating costs are estimated to be about $650,000 to cover services, staffing, targets and materials.

The estimated sales value in Australia of cyclotron-produced radioisotopes, based on current usage patterns, is $1.15 million. Details are given in Table 5 for the commonly used products. In the case of gallium-67 and thallium-201 which are imported at present, the figures represent the actual consumption. Figures for the other products are estimates, based on conservative assumptions, obtained from nuclear physicians.

For comparison, usage in the USA is given in Table 6. Comparing these statistics with those for the estimated Australian consumption on a per capita basis, the USA spends more than twice the predicted Australian figure on cyclotron radioisotopes. The difference in the two consumption rates may be taken as an indication of a potential sales growth in Australia.

Optimistically there is no reason why most of the Australian market should not be supplied by the national cyclotron, together with an expanding market in South East Asia and the Pacific. Thus the revenue should be significantly greater than the operating costs (excluding amortisation of capital investment).

In the USA and Europe, cyclotrons are operated commercially at a profit after taking into account both capital and operating costs. This situation could not apply in Australia because of the limited market.

TABLE 5
ESTIMATED SALES IN AUSTRALIA OF
CYCLOTRON PRODUCED RADIOISOTOPES

Radionuclide	Australian Usage per Annum, mCi	Average Selling Price per mCi $	Annual Revenue $
Gallium-67	22,000	8.6	189,000
Iodine-123	1,800	92*	166,000
Thallium-201	12,000	52	624,000
Indium-111	300	65	20,000
Krypton-81m	4,200*	35*	147,000
Estimated Total Annual Revenue			1,146,000

*Estimated from US market statistics

TABLE 6
THE ESTIMATED MARKET SIZE FOR CYCLOTRON
RADIOISOTOPES IN THE USA

Radioisotope	Total Sales mCi	Annual Revenue $
Gallium-67	925,000	4,700,000
Thallium-201	800,000	26,400,000
Indium-111	11,400	800,000
Iodine-123	58,700	5,400,000
Krypton-81m	62,700	2,200,000
Total Market		39,500,000

(B) Nuclear Medicine/PET Centre

Taking AINSE as a model, it is estimated that the notional operating costs would be of the order of $0.5-1 million of which half would be provided by the Commonwealth and half by the participating medical organisations from all Australian States. This would provide the salaries for a core of permanent staff (many of whom could be expected to come from the existing AAEC complement) and running costs for research, conferences, training and clinical evaluation. Attached clinical research staff are expected to be funded by their own organisations. Although ground rules for operating such a cooperative centre have been drawn up along AINSE lines, the details require further discussion between the participating bodies.

8. BENEFITS

Medical

Production of cyclotron radioisotopes on a routine basis from the national cyclotron would provide nuclear medicine departments within Australia with the full range of radioisotopes vital to the early diagnosis and treatment of a wide range of medical conditions including cancer, coronary heart disease, strokes and severe trauma. Without this domestic cyclotron capability and the derived clinical benefits, the Australian community is deprived of a basic component of health care enjoyed for many years by people in all other countries of comparable development. An added benefit is the reduced radiation dose to patients and staff from the use of certain cyclotron products.

The national nuclear medicine/PET centre in association with the medical cyclotron offers the following benefits;

(a) The Centre could be a national research centre of international repute, to obtain new scientific insights into fundamental biochemical and physiological processes vital to a proper understanding of the physiology of disease.

(b) As a national focus of PET research in Australia it would ensure improved access to the results from overseas PET centres thereby ensuring the rapid application of new knowledge throughout Australian medical practice.

(c) The Centre could have an important training function for physicians, chemists, physicists and technologists employed in nuclear medicine throughout Australia and in the near geographic region - perhaps in conjunction with the Sydney-based Australian School of Nuclear Technology.

(d) The Centre could evaluate the potential clinical applications of the new expensive imaging technologies, e.g. PET and perhaps NMR, develop operational and training procedures, and promote standards and the national dissemination of information, prior to the more widespread deployment of these technologies throughout Australia. This would allow better control of expenditure on high technology health care.

PET is already being used, for example;

- to study the normal metabolic pathways involved in sight and hearing;
- to study the behaviour of drugs in neurology and in psychiatric disorders and the disorders themselves;
- to quantify blood flow and oxygen and glucose utilisation, related to pathological conditions;
- to study and demonstrate focal pathophysiology in common conditions such as dementia, stroke and epilepsy;
- to assess the severity of underlying changes in cardiac muscle in patients with heart disease;

- to quantify the degree of lung damage (e.g. from sarcoid infiltration) before and during therapy. It can thereby assess the efficacy of treatment in this and other therapies; and

- to quantify the specific concentration of antibiotics in infected tissues such as lung which could well lead the way in investigating the tissue kinetics of therapeutic agents in general.

A logical further step worthy of consideration is to co-locate a nuclear magnetic resonance facility with the PET facility. NMR scanning, while still at an early stage of development, yields anatomical images of excellent resolution and also has application for biological tracing to study regional tissue function. If housed together they would provide complementary information as well as being evaluated against each other.

In a commissioned report dated October 1983 prepared for the Committee on Appropriations of the Senate of the USA entitled, 'An Evaluation of Research Opportunities and Needs of NINCDS (National Institute of Neurological and Communicative Disorders and Stroke' it is noted:

> 'The PET technique helps us to visualize the metabolism and function of the brain by displaying chemical reactions and correlating these reactions with brain activity. Thus, it provides an intimate look at the machinery of the living human brain in action. Recognizing the extraordinary opportunity offered by PET, the Congress of the United States enabled NINCDS to fund a number of research centers for the applications of PET to brain research. There are currently 10 such centers in the United States.
>
> Now another imaging approach has become available. It relies on NMR (nuclear magnetic resonance) spectroscopy and utilizes the principle that the nuclei of certain types of atoms behave like miniature magnets which, when placed in high-intensity external magnetic fields, can be induced to transmit signals capable of being imaged as in CAT and PET. NMR has the advantage of utilizing

the brain's own chemicals. It does not need X-rays or radioisotopes. Its resolution is finer than that of PET, so it can be used to examine smaller volumes of tissue and perhaps even to visualize molecular arrays. And because its image develops almost instantaneously, NMR permits minute-to-minute monitoring of chemical and physiological events, in place of the periodic samplings obtained by PET. ***NMR is not capable, however, of addressing all questions. It cannot, for example, localize drugs or antibodies. But a complementary mix of PET and NMR scanning is likely to produce optimal exploitation of imaging capabilities.** Already, these techniques have provided a wealth of previously unsuspected information about stroke, head injury, multiple sclerosis, Huntington's disease, Alzheimer's disease, aphasia, and dyslexia, to mention just a few examples. No wonder neuroscientists, basic and clinical alike, are excited by the prospects.' (*Author's emphasis)

Economic

Confidence exists, in the terms described in Section 7, that although an Australian cyclotron would not recover both capital and operating costs (as for commercial radioisotope production cyclotrons in larger countries), the market in Australia and the near geographic region, estimated conservatively as $1.15 million annually, is sufficient for a domestic cyclotron to offset its annual operating production costs of about $0.65 million.

Allied to this, a domestic capability to produce cyclotron products would remove the present dependence on overseas supply of certain longer-lived cyclotron radioisotopes presently worth $0.75 million (and increasing) and the requirement for foreign exchange for this purpose. It would also provide income through sale of the products to New Zealand and South East Asian countries.

Technology

A useful spin-off could be expected from the stimulation of the technologies associated with such a project, e.g. electronics, instrumentation and control, computers and data handling, radiochemistry and remote handling, as well as the stimulation of technologies from the significant rise in the level of nuclear medicine activity throughout Australia; the latter could perhaps include a commercial enterprise for the radioactive labelling of monoclonal antibodies. Industrial applications of cyclotrons and cyclotron products also, must not be overlooked.

9. ROLE OF THE AUSTRALIAN AEC

The AAEC, through its Isotope Division, established a radioisotope advisory service in 1957 and commenced the production of radioisotopes, primarily for industrial application, in 1960. This activity, however, was relatively small until the late 1960s when **in-vivo** diagnostic medical techniques using technetium-99m were introduced into Australia. This together with associated problems with imports, made domestic production of a wide range of isotopes highly desirable.

The provision of radiopharmaceuticals to hospitals throughout Australia by the AAEC enabled the community to enjoy the technological advantages available in other countries. The AAEC developed a nationwide distribution system which made technetium-99m available to each State. In this environment Australian nuclear medicine flourished and the total service became a model to be adopted by other countries.

With the technological advances of the 1970s Australian nuclear medicine began to be overtaken not only by the wealthy and more avanced countries but also by those less well endowed with resources and necessary expertise. This change of situation occurred partly because of the limited availability of cyclotron-produced radioisotopes in Australia.

Over the last 15 years the concept of a cyclotron facility in Australia has attracted the support of individual physicians, scientists and organisations. Several specific studies on this subject involving the AAEC either directly or indirectly have been carried out. These are documented elsewhere. (5)(6)

Following a re-alignment of the AAEC program to accord with changed government priorities, the revised AAEC program gives increased priority to the medical applications of nuclear science and technology for the benefit of the Australian community.

It is in this context of a renewed commitment to support nuclear medicine in Australia that the present proposal for a national cyclotron for radioisotope production is being put forward. The AAEC has had a long experience in the operation of nuclear facilities in general and the processing and distribution of short-lived radioisotopes in particular. It is therefore appropriate for the Commission to own and operate a national cyclotron facility for radioisotope production and distribution to complement its existing operations. It would be inappropriate for this to be done elsewhere in Australia as this would involve duplication of the complex and expensive infrastructure already existing at Lucas Heights.

In regard to the nuclear medicine/PET centre, it would make good sense that this should be established along the lines of the Australian Institute of Nuclear Science and Engineering with the AAEC as the host organisation. The actual organisation of the Centre could be based on the findings of the Advisory Committee convened by the AAEC in 1979 which supported the concept of an Australian Institute of Radiation and Health Medicine (AIRMAH) and the need for a national cyclotron. This committee included representatives of the AAEC, AINSE, the Commonwealth Departments of Health (ARL and NH&MRC) and National Development and Energy, University Medical Schools and Hospitals.

The proposal developed by this Committee was for AIRMAH to be an unincorporated association with the following foundation members:

Commonwealth Department of Health
National Health and Medical Research Council
Australian Atomic Energy Commission
Universities with medical schools from all States.

It was also proposed that funds be provided by the States and Commonwealth on a dollar for dollar basis with each State contributing according to the number of medical schools. A Council would administer policy and the research programs with operational management by the AAEC. The adjacent teaching hospital would be one of the members with no preferential rights over those of other members.

The AAEC could be expected to play a key role in providing the non-medical scientific expertise to the research, evaluation and training activities of the nuclear medicine/PET centre. This recognises that an effective PET centre requires a multidisciplinary team of clinical researchers, physicists, radiochemists, mathematicians, computer scientists, physiologists, pharmacologists, biochemists, referring clinicians, and cyclotron operators, engineers and technicians.

10. LOCATION

If the national medical cyclotron were to be limited in scope to producing only those radioisotopes which can be distributed Australia-wide, then it should be located at Lucas Heights to make maximum use of the facilities already in existence for the production, processing and distribution of reactor-produced radioisotopes. Such a decision would be short-sighted since it would limit the future medical benefits that could derive from the cyclotron and would not make full use of the cylotron.

Rather, it is considered highly desirable to have the dual purpose flexibility to make maximum use of the cyclotron for advanced medical studies and training.

It is therefore proposed that the National Medical Cyclotron Facility be located:

(i) at a major university teaching hospital with nuclear medicine facilities, specialised diagnostic services, academic units and a large patient load;

(ii) adjacent to a university campus to promote interactions with staff who have essential expertise; and

(iii) as close as possible to Sydney Airport and Lucas Heights to take advantage of the special nuclear and high technology skills of the AAEC and the existing complementary production and distribution service based on reactor products.

Following discussions between the AAEC and the Royal Prince Alfred Hospital (RPAH), the Chairman of RPAH has indicated agreement in principle to provide land for the cyclotron installation.

11. CONSULTATION

Consultation at this stage has been primarily with medical specialists in the Sydney area, the Australian and New Zealand Association of Physicians in Nuclear Medicine, the Australian and New Zealand Society for Nuclear Medicine and overseas organisations with experience in operating medical cyclotrons, as well as with relevant government departments.

The proposal has a high degree of support as evidenced by the letters copied at Appendix 1 from:

- The Nuclear Medicine Coordinating Committee of Western Australia.

- Professor L J Peters, Head, Division of Radiotherapy, M.D.Anderson Hospital and Tumour Institute, Houston, Texas.

- Professor John E Turtle, Head, Department of Endocrinology and Professor of Medicine, Royal Prince Alfred Hospital.

- The President of the Australian and New Zealand Association of Physicians in Nuclear Medicine.

- Professor A Syrota, Service Hospitalier Frederic Joliot, Commissariat a l'Energie Atomique, Paris.

- Professor H N Wagner, Director, Divisions of Nuclear Medicine and Radiation Health Sciences, The John Hopkins Medical Institution, Baltimore.

- Professor David Kuhl, Department of Radiological Sciences, UCLA Medical Center, Los Angeles.

- Professor S James Adelstein, Prof. of Radiology and Dean for Academic Programs, Harvard Medical School, Boston.

12. ACKNOWLEDGEMENTS

This paper was prepared with advice and assistance from the following people.

AAEC Laboratories, Lucas Heights

Dr C J Hardy, Chief Isotope Division
Mr R E Boyd, Head, Radioactive Products Research Section
Mr K W Horlock, Controller, Commercial Products Unit
Mr R McAneny, Leader, Production Works & Maintenance Section
Dr B Allen, Nuclear Physics Group

Royal Prince Alfred Hospital

Dr J G Morris, Director, Department of Nuclear Medicine
Dr G J Bautovich, Physician in Nuclear Medicine
Mr B F Hutton, Chief Physicist
Mrs J E Towson, Physicist

A particular acknowledgement is due to Dr John G Morris, who has persistently pursued for more than a decade the quest for a medical cyclotron for Australia.

13. REFERENCES

1. A report to the IAEA, on the feasibility of cyclotron facilities, Terry Jones, MRC Cyclotron Unit, Hammersmith Hospital, UK, July 1984.

2. Application of Cyclotron-produced radioisotopes, M Quinlan - this workshop.

3. Current applications of positron-emission tomography (PET) E J Potchen - this workshop.

4. Potential applications of PET in Australia, A E Doyle - this workshop.

5. The medical case for an Australian National Cyclotron, J G Morris et al - submitted to the Medical Journal of Australia.

6. AAEC critique of NHTAP report on medical cyclotron facilities, October 1984.

THE NUCLEAR MEDICINE CO-ORDINATING COMMITTEE OF WESTERN AUSTRALIA

ESTABLISHMENT OF A CYCLOTRON RESEARCH FACILITY IN AUSTRALIA

There is no cyclotron in Australia. In contrast, developed countries with a comparable population, such as Belgium or Holland, each have three major cyclotron research establishments.

Australian scientists are denied the opportunity to participate in research in cyclotron applications in the biological, physical, chemical and medical sciences. The nonavailability of short lived cyclotron produced radioisotopes such as oxygen-15, carbon-11, nitrogen-13 and fluorine-18 precludes basic physiological and pharmacological research utilizing positron emission tomography.

Australian nuclear physicians are totally dependant on overseas supplies of longer lived cyclotron-produced radioisotopes such as gallium-67 for diagnosis of cancer and infection,and thallium-201 for diagnosis of heart disease. These supplies are expensive and unreliable and are insufficient for wide research application.

The nuclear physicians of Western Australia wish to strongly recommend the establishment of a cyclotron research facility under the aegis of the Australian Atomic Energy Commission. The cyclotron may be located in Sydney and would be accessible to all scientists in Australasia. It should incorporate adequate provision for research and development in radiochemistry and radiobiology, as well as medical research applications in positron emission tomography. Such a facility would also be expected to provide longer lived cyclotron-produced radionuclides for Australasia and Oceania and relieve the current total dependence on overseas suppliers.

Australian nuclear scientists are being left behind and we request your urgent attention to provision of adequate facilities to support research and development in Australia in this field of rapidly advancing high technology.

Frederic T A Lovegrove

Agatha A van der Schaaf

Michael F Quinlan
(Chairman)

J Harvey Turner

Vincent Antico

Ivor Surveyor
(Secretary)

The University of Texas System Cancer Center

M. D. Anderson Hospital and Tumor Institute
Texas Medical Center • 6723 Bertner Avenue • Houston, Texas 77030

RADIOTHERAPY

January 30, 1984

Professor Max Brennan
Chairman
Australian Atomic Energy Commission
Lucas Heights Research Laboratories
Private Mail Bag
Sutherland, N.S.W. 2232
AUSTRALIA

Dear Professor Brennan:

RE: Acquistion of a Cyclotron in Australia

As you know, Dr. John Morris visited this Institution December 21, 1983, as part of a fact-finding tour of cyclotron installations in various parts of the world. My understanding was that Dr. Morris would be reporting back to the Australian Atomic Energy Commission at about this time, and I, therefore, felt it appropriate to convey my thoughts on the subject of a medical cyclotron in Australia.

Acquisition of a cyclotron of appropriate energy would offer two new capabilities to Australian medicine: 1) production of short-lived isotopes, particularly positron emitters for use in nuclear imaging, and 2) capability for fast neutron radiotherapy. With regard to the first function, the present limitation of available isotopes in Australia today to those produced in a nuclear reactor presents a serious impediment to the practice of nuclear medicine. It should, in fact, be recognized as a severe embarrassment that a country as affluent as Australia does not have a cyclotron for isotope production purposes. As I am sure Dr. Morris will forcefully point out, very active research using short-lived positron emitting isotopes is ongoing in many different parts of the world at the present time and the imaging capabilities being developed offer a unique new technology for non-invasive monitoring of human physiology and metabolism.

Regarding fast neutron radiotherapy, the argument for providing this capability in Australia is less compelling since the place of high LET radiotherapy has not yet been clearly defined. However, one can say that it is almost axiomatic that certain tumors would be better treated with high LET radiations than with conventional treatment, and conversely it is equally axiomatic that some tumors would be adversely affected by high LET therapy. There is general

Professor Max Brennan January 30, 1984

agreement at the present time that the most important task facing radiotherapists with fast neutron capability is the identification of patients predictively who will benefit from such therapy. I personally feel optimistic that suitable predictors will be forthcoming, and that neutron therapy will find an important role in clinical radiotherapy.

In summary, it seems to be that acquisition of a cyclotron for isotope production is long overdue in Australia and I would strongly support such an initiative. The instrument should be located in a major teaching hospital so that short-lived isotopes can be generated and used clinically. Whether the option for fast neutron radiotherapy should be provided would hinge on a large extent on the recruitment of an academic radiotherapist to direct a program of clinical research.

At the request of Dr. Morris, I am enclosing herewith parts of the grant application which was the basis of our generating funds to acquire a dual purpose cyclotron for this institution. Please note that the grant was written in 1977 and is in places out of date, but the general thrust of the application is valid. Also I enclose a copy of the latest progress report on the cyclotron project that was submitted two months ago. This sets out some of the problems encountered in the installation of the UT M. D. Anderson instrument.

Sincerely yours,

Lester Peters

Lester J. Peters, M.D.
Professor and Head
Division of Radiotherapy

LJP/bf
Encl.

cc: Dr. John Morris

The University of Sydney
Department of Medicine

SYDNEY, N.S.W. 2006

13th March, 1984.

Dr. R. Smith,
Deputy Director,
Australian Atomic Energy Commission,
Lucas Heights,
New South Wales.

Dear Dr. Smith,

RE: IODINE I-123 IN THYROID DIAGNOSIS

Iodine I-123 has less neutrons than I-131 thus the isotope is unstable and tends spontaneously to transform towards the more stable arrangement. For most purposes iodine I-123 is an ideal isotope for in vivo diagnostic studies of thyroid structure and function. Its half-life is 13.3 hours with a 28 keV X-ray and a 159 keV gamma ray emission in essentially equal quantities. It has no beta emissions. The ratio of detectable photons to radiation dose is high and the short half-life is suitable for routine uptakes and scans.

Thyroid uptake with a ratio of the counting ratio of the two photons can be performed at 20 minutes after an intravenous dose or at 1 - 24 hours after an oral dose. A high resolution scan is possible with either photon as early as 20 - 30 minutes after a large dose of the isotope. With 50 - 100 uCi doses given orally, scans superior in resolution to those afforded by Technetium ^{99}mTc or I-131 can be obtained at 6 hours after the administration, the absorbed radiation dose being about 185th that for an I-131 study.

The isotope of choice in children is iodine I-123 which has all the advantages of I-131 and also minimises the radiation dose to the thyroid.

Iodine I-123 is the agent of choice for imaging and uptake measurements, comparing favourably with absorbed radiation doses in thyroid scanning with I-131 (thyroid 7.5 -v- 800 rads/mCi: total body 0.027 -v- 0.47 rads/mCi). The short half-life of I-123 iodine precludes its use in body scanning for metastasis or follicular carcinoma of the thyroid. Most authors consider that iodine I-123 is nearly ideal for routine uptakes and scanning purposes both in children and adults.

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Nishiyama, N. et al. Journal of Nuclear Medicine, 15: 261, 1974.

Wellman, H.N. et al. Seminar Nuclear Med, 1: 356, 1971.

Yours sincerely,

JOHN R. TURTLE, MD, FRACP
Professor of Medicine
Head, Department of Endocrinology (Medical)
ROYAL PRINCE ALFRED HOSPITAL

AUSTRALIAN AND NEW ZEALAND ASSOCIATION OF PHYSICIANS IN NUCLEAR MEDICINE

Dr. I.H. Buttfield,
Department of Nuclear Medicine,
The Queen Elizabeth Hospital,
Woodville Road,
WOODVILLE S.A. 5011

15th June, 1983

Dr. N. Blewett,
Minister for Health,
C/- Parliament House,
CANBERRA A.C.T. 2600

Dear Sir,

An ad hoc committee of members of the Australian and New Zealand Association of Physicians in Nuclear Medicine from N.S.W. has put forward a proposal to yourself for a national medical cyclotron facility to be run by the Australian Atomic Energy Commission. I write to endorse and support this proposal on behalf of the national body of this Association and indicate that we believe such a proposal to be in the interests of patients with a range of diseases requiring investigation including cancer, coronary artery disease, strokes and severe trauma, and in the national interests.

To support the development of a national cyclotron facility, we feel that the following major points of principle are worth consideration in any deliberations on this subject:

a. There is considerable public benefit from the developments of such a facility, not only to the patients who may be treated or for the money saved by the taxpayer, but also to the community as a whole, through the orderly development of peaceful uses of nuclear technology for health, since the materials used in the cyclotron are not part of the uranium cycle.

b. There is a considerable long term benefit, since the cyclotron once installed, will last many decades. The available figures suggest that a cyclotron will save some overseas expenditure in the short term and may become a significant foreign income earner in the long run.

c. The radioactive materials made by this machine has an established place in the current Nuclear Medicine practice and can be used to reduce the discomfort of many diagnostic procedures and in many cases, may reduce the exposure to radiation of patients undergoing investigation. Further, this machine may have a major role in the treatment of certain types of diseases, particularly cancer.

/2.

My Association believes that there is a very real and urgent need for a cyclotron in Australia for enhancing patient care and that such a machine is now well and truly justified.

I trust that you will be able to support this submission. This Association would be only too pleased to discuss any relevant matters with you or your officers in any way that you see fit.

Yours faithfully,

I. Buttfield

DR. I.H. BUTTFIELD
President

SERVICE HOSPITALIER
FRÉDÉRIC JOLIOT

Tél. : (6) 908. 77. 01
DB/SHFJ 84.453 AS/nd

COMMISSARIAT A L'ÉNERGIE ATOMIQUE
Département de Biologie

Doctor John MORRIS, F.R.A.C.P.
Director - Dept. of Nuclear Medicine
ROYAL PRINCE ALFRED HOSPITAL
Missenden Road,
Camperdown,
N.S.W. 2050
AUSTRALIA

Orsay, September 12th, 1984

Dear Dr. Morris,

Thank you very much for asking me to comment your proposal for an Australian National Cyclotron.

I have noted the key features of this proposal and my opinion is that there is no doubt that such a facility is a necessity for Australia. The use of ^{123}I is in rapid development for labeling biological molecules, as ^{201}Tl for cardiologic applications ; the acquisition of a cyclotron will allow their production and distribution across the country. Furthermore, I know personnally several physicists and MDs working in Nuclear Medicine in Australia, they are all very active in this field and the limitation in available isotopes limit their possibilities. It is also well known now that Positron Emission Tomography offers a unique possibility in studying noninvasively brain and heart metabolism and receptors in man ; the cyclotron will provide the short-lived radioisotopes. However, I would point out a difficulty which can occur when a cyclotron (40 MeV proton machine) is used for several purposes : production of long-lived radioisotopes, neutron radiation therapy and production of short lived radioisotopes. You know that different constraints are attached to each of these applications and it is more difficult to run such a machine than a cyclotron dedicated to a single application. The example of the Hammersmith Hospital in London (MRC cyclotron unit) proves that it can work very well but possible difficulties should be kept in mind.

In conclusion, I am convinced, that the acquisition of a cyclotron in Australia is an absolute and urgent necessity and the report you sent me shows clearly that the support needed for its development exists in your country.

I am at your disposal whenever you want if you need more detail concerning the PET and NMR spectroscopy facility at the Service Hospitalier Frédéric Joliot.

Sincerely yours,

A. SYROTA, M.D., Ph. D.
Professor of Nuclear Medicine
and Biophysics

THE JOHNS HOPKINS MEDICAL INSTITUTIONS

DIVISIONS OF NUCLEAR MEDICINE AND RADIATION HEALTH SCIENCES

ORTH WOLFE STREET
IMORE, MARYLAND 21205-2179

Telephone 301; 955-3350

September 27, 1984

Professor Max Brennan
Chairman, Australian Atomic Energy Commission
Private Mail Bag
Sutherland 2232 N.S.W.
Australia

Dear Professor Brennan:

I am happy to accept the invitation to comment on the document DR 16 describing the casd for a national medical cyclotron in Australia, prepared by R. Smith, C.J. Hardy and R.E. Boyd.

In essence, I strongly support the concept that the AAEC establish a medical cyclotron facility. The advances that are being made today with cyclotron-produced radionuclides, especially carbon-11, fluorine-18 and iodine-123, are outstanding and cannot be achieved without the sensitivity that measurement of radioactivity provides. For example, it is now possible to examine the concentrations within the living human brain of neurotransmitters and neuroreceptors that are of a major importance in normal brain function and are involved in important neuro-psychiatric disorders such as schizophrenia, Parkinson's disease, Huntington's disease, depression and drug addiction. Just as the sensitivity of radioimmunoassay revolutionized the measurement of peptide hormones present in picomolar concentrations in the blood and other body fluids, so also does the use of positron-emitting tracers permit the same sensitivity to be applied to the study of in vivo chemistry of organs, including the brain, heart and lungs.

I believe that it is of the greatest urgency that a cyclotron facility be placed in at least one major medical center so that carbon-11, fluorine-18 and oxygen-15 can be produced. This should include at least one positron-emission tomography system.

I am not able to say whether a large cyclotron that can be used for the produciton of both short-lived radio-nuclides such as carbon-11 and iodine-123 could be close enough to a major medical center to serve local needs and provide material for shipping. I hope that it is possible. If possible, medical cyclotrons should be in hospitals and not out in the countryside. If this is impossible, there should be a large Lucas Heights' size cyclotron coupled to small medical cyclotrons in major medical centers. Technical support would be from Lucas Heights.

Received 9-10-84

We at Hopkins believe that NMR and PET should both be developed. In essence, the major advantage of NMR is superb anatomical information with no ionizing radiation. This makes possible multiple studies in the same persons, including children. Although chemical studies are possible with NMR, they have a 10^6 to 10^{14} disadvantage in sensitivity compared to PET. NMR cannot be used to study receptors and drugs the way PET can. It makes no more sense to me to try to decide between NMR and PET than it does to try to decide whether a medical school should have a department of surgery or a department of medicine.

PET and NMR are ideas whose time has come. It would be a shame if Australian medicine reaches this turning point and does not turn.

These are general comments. I'm sure you want more specifics. I'm happy to do all I can to help. You and your colleagues are welcome to come at any time to see what interesting results we are getting with dopamine, opiate and other neuro-receptors.

Best regards,

Yours sincerely,

Henry N. Wagner, Jr., M.D.
Professor of Medicine, Radiology
and Environmental Health Sciences
Director, Divisions of Nuclear Medicine
and Radiation Health Sciences

mac

cc: John Morris

NIVERSITY OF CALIFORNIA, LOS ANGELES UCLA

KELEY · DAVIS · IRVINE · LOS ANGELES · RIVERSIDE · SAN DIEGO · SAN FRANCISCO SANTA BARBARA · SANTA CRUZ

DEPARTMENT OF RADIOLOGICAL SCIENCES
UCLA MEDICAL CENTER
CENTER FOR THE HEALTH SCIENCES
LOS ANGELES, CALIFORNIA 90024

29 October 1984

Professor M. Brennan
Chairman
Australian Atomic Energy Commission
Private Mail Bag
Sutherland NSW 2232
Australia

Re: National Medical Cyclotron

Dear Professor Brennan:

I send you this in support of your March 1984 AAEC proposal for a National Medical Cyclotron.

In December 1983 Dr. John Morris visited us at UCLA and explained some of the intentions to meet aspirations in Australia for the use of very short-lived radionuclides and for pushing the frontiers in Nuclear Magnetic Resonance Spectroscopy. Subsequently, I have received a copy of the Lucas Heights proposal which includes provision for a National Cyclotron to be placed in a Sydney University teaching hospital and for planning to follow concerning establishment of positron emission tomography and NMR Spectroscopy.

I congratulate you on mounting this program. Your approach seems sound. This project should not only equip Australian scientists to play important roles in the advance of new knowledge, but is also likely to be in direct support of patient care.

Respectfully,

David E. Kuhl

David E. Kuhl, M.D.
Professor of Radiological Sciences

DEK:cl
cc: Dr. John Morris,

HARVARD MEDICAL SCHOOL DEPARTMENT OF RADIOLOGY
JOINT PROGRAM IN NUCLEAR MEDICINE
BETH ISRAEL HOSPITAL • BRIGHAM & WOMEN'S HOSPITAL •
DANA-FARBER CANCER INSTITUTE • THE CHILDREN'S HOSPITAL

AHC.516 - 4

October 15, 1984

Professor Max Brennan
Chairman AAEC
Private Mail Bag
Sutherland NSW 2232
AUSTRALIA

Dear Professor Brennan:

Professor John Morris (by post) and Dr. Clarence Hardy (by visit) have shared with me the AAEC Report on an Australian National Cyclotron.

I find the Report of considerable interest as it provides members of the Australian Nuclear Medicine community with the potential of retaining a world leadership position in their field.

Of the general findings, I would comment specifically on two:

1. That the cyclotron produce ^{111}In, ^{123}I (pure) ^{67}Ga and ^{201}Tl as well as positron-emitting radionuclides. Current clinical use and the potential for emission tomography with unpaired electrons in the fields of cardiology, oncology and infectious disease makes this capability very important. In addition, the prospects for labelling specific receptor sites and immunoglobulins are extremely bright and this technique is likely to provide useful clinical information as well as insights into human (and animal) diseases.

2. The cyclotron should be located in a clinical facility so that research with carbon-11, oxygen-15 and nitrogen-13-labelled compounds can be pursued with minimum patient inconvenience. If the full potential of positron emission tomography (PET) is to be realized, some groups of patients, too ill to be moved, must be included. Moreover, the tight collaboration required between medical physicists and engineers, on the one hand, and physicians and biomedical scientists on the other, require that they be proximate. With this arrangement the cyclotron can also be used to provide fluorine-18-labelled compounds to medical centers with PET tomographs located at some distance.

DIVISION OF NUCLEAR MEDICINE · BRIGHAM & WOMEN'S HOSPITAL
75 FRANCIS STREET · BOSTON, MASSACHUSETTS 02115 · (617) 732-5500

Received 26-10

Professor Max Brennan
Chairman AAEC

October 15, 1984

Page 2

It is now clear that the next advances in medical science will rely heavily on observations made in vivo of regional physiology and metabolism. SPECT, PET and NMRI will each have a role. If the reports recommendations are implemented, Australian scientists and physicians will play a central role in these developments.

I appreciate this opportunity to comment on this thoughtful report.

Yours sincerely,

S. James Adelstein, M.D.
Professor of Radiology and
Dean for Academic Programs

SJA:mc
cc: Professor John Morris
Dr. Clarence Hardy