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LUCAS HEIGHTS RESEARCH LABORATORIES

THE CASE FOR A NATIONAL MEDICAL CYCLOTRON

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THE CASE FOR A NATIONAL MEDICAL CYCLOTRON

1. BRIEF OUTLINE OF PROPOSAL

It is proposed that a National Medical Cyclotron and associated radioisotope processing facilities be established to provide Australia and the South East Asian and Pacific Regions with the full range of radioisotopes and radiopharmaceuticals vital to the diagnosis and treatment of a wide variety of medical conditions.

Specifically a national medical cyclotron would be used to produce those cyclotron-produced radioisotopes which cannot be imported because of their short half-lives (e.g. carbon-11, nitrogen-13, oxygen-15, fluorine-18, iodine-123, rubidium-81, mercury-195m), and also those of longer half-life which are imported at substantial cost (about $0.75 million in 1983) on a rather unreliable basis (e.g. gallium-67, thallium-201, indium-111). These cyclotron-produced radioisotopes (with the exception of iodine-123 to replace iodine-131) are complementary to the range of reactor-produced radioisotopes available from the Australian reactor HIFAR. Where feasible in terms of radioisotope lifetime, the products from the cyclotron would be distributed Australia-wide, and also to the immediate geographical region, using the Australian AEC distribution service already available for reactor-produced products.

To take full advantage of the potential medical benefits, the cyclotron would be located in NSW at a major teaching hospital, provisionally the Royal Prince Alfred Hospital, Sydney, but it would be owned and operated by the Australian Atomic Energy Commission. Installation could be completed in 1987/88 at a cost of about $10 million. Funding of $200,000 is sought in 1984/85 for the preparation of detailed plans and specifications.

2. NUCLEAR MEDICINE* IN AUSTRALIA

Nuclear medicine facilities exist in some 50 hospitals throughout

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* Nuclear medicine has been defined recently by the American Society of Nuclear Medicine (February 1983) as 'the medical speciality which utilises the nuclear properties of radioactive and stable nuclides to make diagnostic evaluations of the anatomic and/or physiological conditions of the body and to provide therapy with unsealed radioactive sources'.

Australia, using radioisotopes as biological tracers for non-invasive early diagnosis of functional disorders in some 200,000 patients annually. Short-lived radioactive substances constitute the safest, most sensitive and effective tracers available for the in-vivo study of biological processes in man and the detection of disease at the earliest possible time. Other diagnostic techniques such as computerised tomography (CT) scanning provide precise anatomical information but they do not give the functional and dynamic data obtainable by using radioisotopes. The provision of functional data allows diagnosis to be made at a reversible stage before permanent anatomical change, thereby enhancing the possibility of a cure.

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 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 concentrate in particular organs or tissues, where they can be detected and visualised by cameras or scanning equipment.

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 1983, the Commission supplied radioisotope products to the value of $2 million (40,000 shipments); of this total more than $1.7 million came from medical applications.

Today nuclear medicine is a well established medical speciality which is accepted as an important and integral part of the overall health care system. 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 standard of the service that can be provided today is significantly below that of most other developed countries. This is because of the lack of an Australian cyclotron and guaranteed access to cyclotron-produced isotopes for specific diagnoses.

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 (e.g. for technetium-99m with a half-life of 6 hours) the national need is 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 supply is both unreliable and ineffective for gallium-67, thallium-201 and indium-111 which have half-lives of about 3 days.

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 or effectiveness. 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 a very much higher radiation exposure to the patient; this deficiency could be corrected with the installation of an Australian medical cyclotron.

3. CYCLOTRONS FOR NUCLEAR MEDICINE

In nuclear reactors, radioisotopes are produced by bombardment 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 it 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). Appendix A lists cyclotrons in operation or on order throughout the world which are primarily used for medical purposes. 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. Appendix A and Figure 1 show that there are some 90 cyclotrons in use for

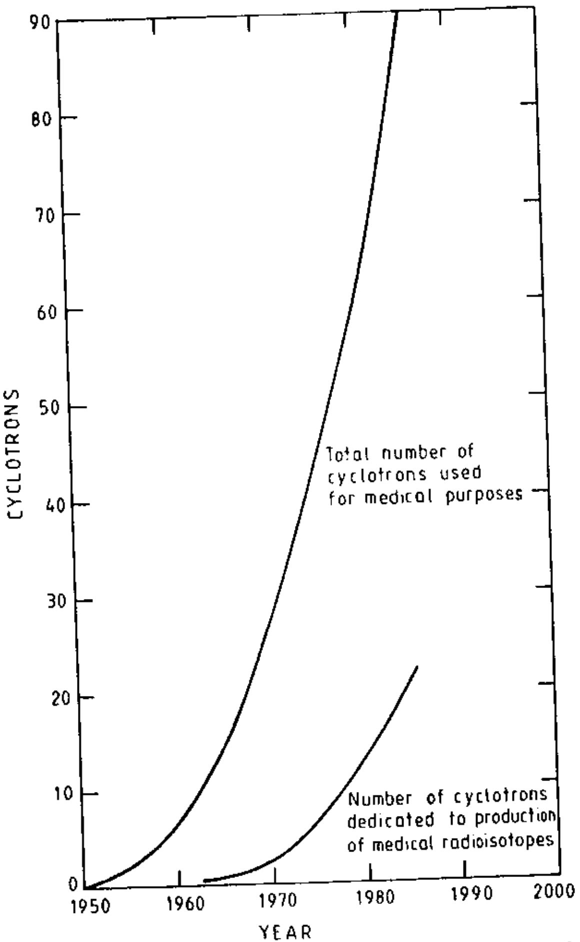


Figure 1 GROWTH IN NUMBER OF CYCLOTRONS FOR MEDICAL PURPOSES

medical applications and that the number has increased dramatically in recent years. 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. The medical applications and benefits are considered in Section 4. In total there will be 21 installations by 1985 (e.g. UK - 2, France - 1, Belgium - 1, Japan - 3, USA - 13) installed mainly by such companies as Mallinckrodt, New England Nuclear Medi-Physics, and Amersham Radiochemical Centre.

(b) Cyclotrons primarily for producing PET studies

About 45 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 imaging technique of positron emission tomography (PET) for in-vivo studies of basic physiological processes. This important medical development is considered in some detail in Appendix C. Here it is sufficient to note that the technique requires an on-site cyclotron to produce the positron-emitting, biologic radioisotopes, carbon-11, nitrogen-13, oxygen-15 and fluorine-18, which have very short half-lives of 2 to 110 minutes and, with the exception of ^{18}F, can be used only at their place of production.

(c) Cyclotrons for cancer therapy

Considerable interest has developed in recent years in the use of cyclotrons to produce neutron beams from beryllium targets which 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 some types of cells (hypoxic) 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 type of cancer therapy.

(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.

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 ($T_{\frac{1}{2}}$), the radiation energy (E_γ keV) and data on possible nuclear reactions that can be used for production, with the energy of the bombarding particle, and the production yield.

The radioiosotopes carbon-11, nitrogen-13, oxygen-15 and to some extent fluorine-18 have such short half-lives that they cannot be distributed for general use in Australian hospitals. When used with positron emission tomography they have great potential for health benefit, particularly for clinical research. The production of ultra-short-lived radioisotopes and the provision of PET are not included in the present proposal, but it is a development option that is available in association with the cyclotron (see Appendix C).

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 concentrating in the organs 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. Examples of the medical applications of these radioisotopes are as follows :

Gallium-67 (^{67}Ga)

This radioisotope, in the chemical form of gallium citrate, has a marked tendency to concentrate in tumours and abscesses. The clinical application of ^{67}Ga in the detection of cancer is increasing, particularly as its pattern of

TABLE 1
COMMON CYCLOTRON ISOTOPES OF MEDICAL INTEREST

Radioisotope	$T_{\frac{1}{2}}$	E_{γ} keV	Nuclear Reaction	Energy Bombarding Particle MeV	Production Yield μCi/μA.h
Carbon-11	20.3 min	511	$^{14}\mathrm{N}(p,\alpha)^{11}\mathrm{C}$	15	80,000
			$^{11}\mathrm{B}(p,n)^{11}\mathrm{C}$	20	-
			$^{10}\mathrm{B}(d,n)^{11}\mathrm{C}$	10	16,000
Nitrogen-13	9.96 min	511	$^{12}\mathrm{C}(d,n)^{13}\mathrm{N}$	15	3,000
			$^{16}\mathrm{O}(p,\alpha)^{13}\mathrm{N}$	20	48,000
Oxygen-15	2.03 min	511	$^{14}\mathrm{N}(d,n)^{15}\mathrm{O}$	6	14,000
			$^{16}\mathrm{O}(p,pn)^{15}\mathrm{O}$	27	3,000
Fluorine-18	109.7 min	511	$^{16}\mathrm{O}(^{3}\mathrm{He},p)^{18}\mathrm{F}$	40	5,600
			$^{16}\mathrm{O}(\alpha,pn)^{18}\mathrm{F}$	65	19,000
			$^{20}\mathrm{Ne}(d,\alpha)^{18}\mathrm{F}$	30	10,000
Iron-52	8.3 h	169;511	$^{50}\mathrm{Cr}(\alpha,2n)^{52}\mathrm{Fe}$	90	8
			$^{52}\mathrm{Cr}(^{3}\mathrm{He},3n)^{52}\mathrm{Fe}$	46	50
			$^{55}\mathrm{Mn}(p,4n)^{52}\mathrm{Fe}$	65	160
Gallium-67	78.3 h	93;185;300	$^{65}\mathrm{Cu}(\alpha,2n)^{67}\mathrm{Ga}$	40	160
			$^{68}\mathrm{Zn}(p,2n)^{67}\mathrm{Ga}$	85	430
			$^{nat}\mathrm{Zn}(\alpha,pxn)^{67}\mathrm{Ga}$	40	165
			$^{65}\mathrm{Cu}(\alpha,2n)^{67}\mathrm{Ga}$	40	160
Bromine-77	57 h	239;521	$^{77}\mathrm{Se}(p,n)^{77}\mathrm{Br}$	25	520
			$^{78}\mathrm{Se}(p,2n)^{77}\mathrm{Br}$	24	4,300
			$^{75}\mathrm{As}(\alpha,2n)^{77}\mathrm{Br}$	38	200
Rubidium-81	4.6 h	191 ($^{81m}\mathrm{Kr}$)	$^{81}\mathrm{Br}(\alpha,4n)^{81}\mathrm{Rb}$	50	2,900
			$^{79}\mathrm{Br}(\alpha,2n)^{81}\mathrm{Rb}$	40	2,000
			$^{81}\mathrm{Br}(^{3}\mathrm{He},3n)^{81}\mathrm{Rb}$	40	30
			$^{nat}\mathrm{Kr}(p,xn)^{81}\mathrm{Rb}$	45	15,000
Indium-111	67.2 h	172;245	$^{109}\mathrm{Ag}(\alpha,2n)^{111}\mathrm{In}$	40	200
			$^{112}\mathrm{Cd}(p,2n)^{111}\mathrm{In}$	22	1,035
			$^{111}\mathrm{Cd}(p,n)^{111}\mathrm{In}$	15	515
			$^{110}\mathrm{Cd}(d,n)^{111}\mathrm{In}$	12	117
Iodine-123	13.0 h	159	$^{127}\mathrm{I}(p,5n)^{123}\mathrm{Xe}\rightarrow{}^{123}\mathrm{I}$	60	4,000
			$^{123}\mathrm{Te}(p,n)^{123}\mathrm{I}$	21	440
			$^{124}\mathrm{Te}(p,2n)^{123}\mathrm{I}$	30	40,000
Thallium-201	73.5 h	70;167	$^{203}\mathrm{Tl}(p,3n)^{201}\mathrm{Pb}\rightarrow{}^{201}\mathrm{Tl}$	31	700
			$^{205}\mathrm{Tl}(p,5n)^{201}\mathrm{Pb}\rightarrow{}^{201}\mathrm{Tl}$	46	2,100
			$^{nat}\mathrm{Tl}(p,pxn)^{201}\mathrm{Tl}$	24	85
Mercury-195m	41 h	262 ($^{195m}\mathrm{Au}$)	$^{197}\mathrm{Au}(p,3n)^{195m}\mathrm{Hg}$	34	4,000

abnormal accumulation becomes better understood. Its actual use is the diagnosis of cancer, the delineation of the extent of the disease, the effect of treatment, the determination of remission and the prognosis for the patient. It is being applied to many forms of malignancy, e.g. lymphoma, melanoma, lung carcinoma, hepatoma and a variety of paediatric tumours. Gallium-67 also concentrates in inflammatory sites and therefore it is frequently used in patients with serious hidden infection for whom the alternative diagnostic techniques are inadequate. The principal clinical problems to which ^{67}Ga is applied include, post-operative and hidden abscesses, prosthesis infection, osteomyelitis, chronic inflammatory lung disease and opportunistic infections in patients under immuno-suppressive treatment.

From a single injection of ^{67}Ga it is possible to investigate the whole of the patient's body by following the pattern of distribution of the radioisotope over periods of up to one week post-administration. Similar global examinations are not readily achieved through other diagnostic modalities.

Iodine-123 (^{123}I)

Iodine is an essential element in the diet from which it is avidly extracted by the thyroid gland and converted into thyroxine and thyroid hormone. Radioiodines, in the form of iodide, have long been used to study this process in the human patient in order to discriminate between the several types of thyroid dysfunction and disease. Iodine-123 which has optimal physical properties is the radioisotope of choice for all in-vivo studies of the thyroid.

Many drugs and biochemically active compounds can be labelled by the inclusion, in the compound, of a radioactive iodine atom without loss of biological activity. This is the rationale for extending the utility of ^{123}I to many other diagnostic problems. For example, ^{123}I-labelled amphetamine is used to determine regional cerebral blood flow in patients suffering a stroke or other ischaemic (blood deficient) episode; the technique is equally applicable to children and adults. Iodine-123 labelled hippurate has now replaced the ^{131}I labelled analogue in renal studies and because this results in a very much reduced radiation exposure the test can now be extended to children. Fatty acids have also been labelled with ^{123}I and used to visualise heart muscle metabolism. A most important prospect for the future is the labelling of monoclonal antibodies with ^{123}I for the identification of specific cancers.

Thallium-201 (^{201}Tl)

Thallium-201 is used extensively in patients with heart disease. Thallium, in the thallous ion form, mimics potassium in human biochemistry and, following injection, is taken up preferentially by the oxygenated cardiac muscle. Thallium-201 images of the heart provide information on the effectiveness of the coronary artery, and indicate whether the heart muscle is viable or not, and are useful in the management of patients with heart disease. This critical test is often the only one available and provides information different from that obtained by coronary angiography or electrocardiography.

Thallium-201 investigations also help to assess the adequacy of surgical treatment to improve cardiac blood supply and the clinical significance of arterial stenosis as detected by angiography.

Thallium-201 also has a small part to play in the differential diagnosis of diseases of the thyroid and of the parathyroid.

Indium-111 (^{111}In)

Although Indium-111 has ideal physical properties for scintigraphic imaging it is its biochemical properties which make it the agent of choice for certain clinical investigations. Indium-111 can be chelated with the ligand diethylene triaminopentacetic acid (DTPA), forming an inert marker to measure the flow of the cerebro-spinal fluid (CSF). Its half-life of 68 hours is sufficiently long for it to be used to determine the existence of forms of hydrocephalus where the flow-rate of the CSF is exceedingly slow; this distinguishes it from ^{99m}Tc-DTPA.

In a simpler chemical form, indium chloride, ^{111}In, has been used for the labelling of proteins, monoclonal antibodies, white blood cells and platelets. Through these agents the clinical utility of ^{111}In will expand appreciably and because of a greater diagnostic accuracy it may replace other radioisotope tests.

Krypton-81m (^{81m}Kr)

Several radioactive agents have been used to measure the perfusion of blood through the lungs; this technique provides the means for diagnosing the threat of pulmonary embolism which is the commonest cause of undiagnosed death in Australian hospitals.

Radioactive gases have been widely used for regional pulmonary function studies, the most common being ^{133}Xe. Although the physical half-life of ^{133}Xe is quite long it does not significantly increase the radiation exposure to the patient because the gas is exhaled rapidly following either inhalation or intravenous injection. The unnecessarily long half-life, however, is hazardous to hospital workers and care must be taken to collect and safely store the exhaled breath of the patients. The real disadvantage with ^{133}Xe is its poor radiation characteristics which yield less than optimal scintigraphic images.

The radioactive gas krypton-81m (^{81m}Kr) has both a short half-life (13 seconds) and ideal radiation characteristics for imaging and hence has become the agent of choice for diagnosis of ventilatory disorders of the lungs. Such ventilatory studies are essential for the interpretation of abnormal perfusion studies in pulmonary embolism.

^{81m}Kr is the daughter product of the cyclotron-produced radioisotope rubidium-81 (half-life 4.6 hours) from which it can be readily separated via a generator device.

Mercury 195m : Gold 195m (^{195m}Hg : ^{195m}Au)

An elegant method of studying heart dynamics is by injection of a bolus of a ^{99m}Tc-radiopharmaceutical into a peripheral vein followed by scintigraphic images as the activity passes through the heart for the first time. The six hour half-life of ^{99m}Tc is a major disadvantage and only two or three successive doses may be injected before the residual blood pool radioactivity degrades the images and the radiation dose to the patient becomes unacceptable.

The ideal system for blood flow rate studies is one using a generator in which the parent has a half-life greater than 24 hours and the daughter a half-life of less than 1 minute. In addition the nuclear and chemical properties must be medically acceptable.

Very few such systems exist and, of those that do, the generator system containing mercury-195m : gold 195m fits the requirements best. This system has been successfully used in clinical trials and it will assume importance in radionuclide angiography as an alternative to cardiac catheterisation.

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 will 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.

(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 about 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 of about 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 this form is widely used in the USA where its 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 Australia. 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 ambiguous and thus 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.

There are four manufacturers of cyclotrons suitable for medical purposes - sufficient to ensure competitive tenders. These are listed in Table 2 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 the cyclotrons from each manufacturer are comparable.

TABLE 2
CYCLOTRONS COMMERCIALLY AVAILABLE FOR MEDICAL PURPOSES

Manufacturer	Model	Particle and Energy (MeV) p	 d	 ^{3}He	 ^{4}He	External Beam Current (μA)
Scanditronix, Uppsala, Sweden	MC-16F	17	15	13	17	30-50
	MC-28F	28	14	21	28	30-65
	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 Corporation, Berkeley, USA	CS-22PD	20	11	-	-	60-100
	CV-28	2-24	4-14	6-36	8-28	40-100
	CV-45(a)	12-45	7-24	-	-	50-200
	CP-60(a)	15-60	-	-	-	200
Japan Steel Works, Tokyo	BC168	16	8	-	-	50
	BC1710	17	10	-	-	50
CGR-MeV, Buc, France	325	16	8	-	-	50
	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 = positron d = deuteron

Major Ancillary Facilities

The major ancillary facilities are:

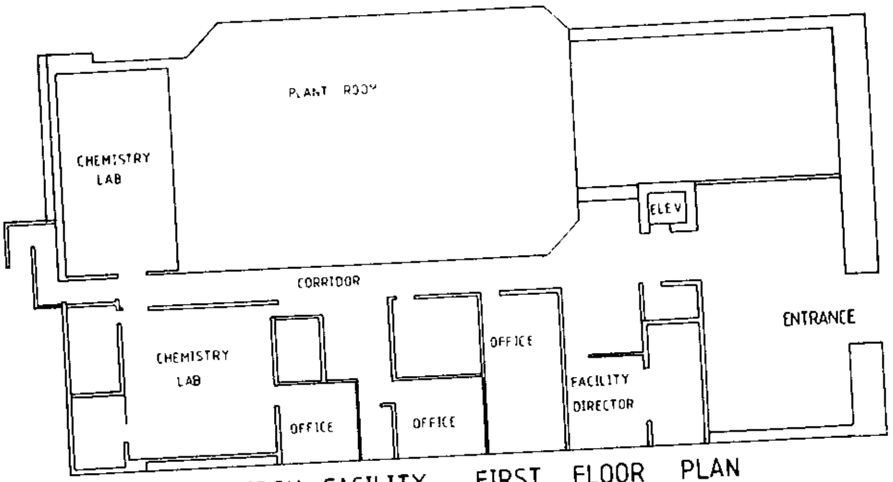
- Beam-handling equipment in the main cyclotron vault to direct beams to target areas (including magnets and computer).
- Shielded and cooled target equipment in shielded cells possibly with a pneumatic tube facility for rapid transportation of products to laboratories.
- Radionuclide processing laboratory 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 radioisotopes would receive final processing into radiopharmaceuticals for nationwide distribution and where benefit would be gained from infrastructure already in existence for radiopharmaceutical production and distribution.
- Electrical and mechanical maintenance workshop.
- Limited packaging and dispatch facilities at the cyclotron site.

One conceptual layout of the proposed cyclotron installation is shown in Figure 2.

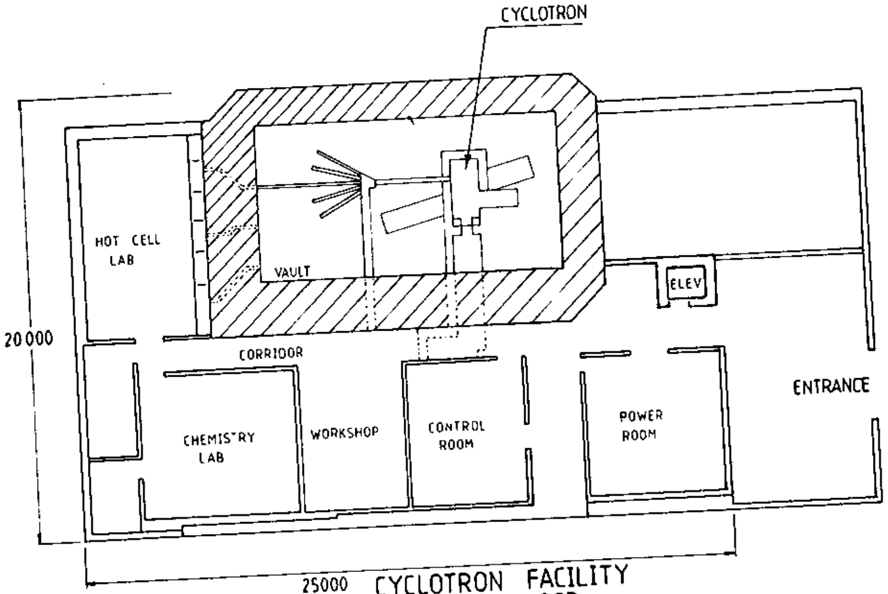
6. RESOURCES REQUIRED

Capital Costs

Preliminary estimates of building and equipment costs at 1984 prices are summarised below for the proposed 40 MeV cyclotron installation. The estimates are based on information provided by cyclotron manufacturers and the operators of some 12 cyclotron installations in North America and Europe. It is assumed that:



CYCLOTRON FACILITY FIRST FLOOR PLAN



CYCLOTRON FACILITY GROUND FLOOR

FIGURE 2. CONCEPTUAL LAYOUT OF THE PROPOSED CYCLOTRON INSTALLATION

(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.

(d) The cyclotron building is two-storey with provision for chemical laboratories and accommodation for operating and processing staff.

(e) No provision has been made for engineering contingencies and the impact of inflation over the construction period.

TABLE 3
CAPITAL COST ESTIMATES

	40 MeV Machine
At RPA Hospital	\$Million
Building (500 m^2 x 9 m containing . Cyclotron vault 15 m x 7.5 m x 4 m with wall thickness of 2.5 m. . Source facilities including power, ventilation, compressed air, cooling water. . Space for laboratories, hot cells and staff.)	6.4
Hot cells (6 off)	0.6
Variable energy cyclotron	2.5
At Lucas Heights	
Extension to processing building 250 m^2 at \$1500/m^2	0.375
Fume cupboards, and processing and dispensing cells and glove boxes	0.125
TOTAL	10.00

Estimated capital expenditure for a 40 MeV cyclotron over the four year construction and commissioning period assuming commitment in 1984/85 would be:

1984/85	1985/86	1986/87	1987/88
\$0.2 M	\$3.0 M	\$5.0 M	\$1.8 M

Operating Budget

The estimated annual operating cost at 1984 prices 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 made up as follows:

TABLE 4

ANNUAL OPERATING COSTS

		\$	\$
Power and Services			70,000
Staffing			
Operators	2	40,000	
Target preparation and processing	2	40,000	
Clerical	1	18,000	
Quality control	2	40,000	
Management and development	2	60,000	
Chemists/production	2	60,000	
Miscellaneous	1	20,000	
Salary overheads		50,000	
Total	12	328,000	328,000
Targets and Materials		250,000	250,000
Total			648,000

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

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

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.

Although some delay can be expected in obtaining approvals from the regulatory authorities of the Department of Health for the sale of Australian products, there is no reason why the whole 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.

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.

7. BENEFITS

Medical Benefit

The proposed facility would provide access within Australia to the full range of radioisotopes vital to the early diagnosis and treatment of a wide variety of medical conditions including cancer, coronary artery disease, strokes and severe trauma. Without such a facility 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. Improved health care is the major justification for the cyclotron installation. This is further supported by the reduced radiation dose to patients and staff that results from the use of certain cyclotron products.

Reduced Radiation Dose

A cyclotron-produced radioisotope may be the agent of choice for a particular diagnostic investigation because of the lower radiation dose it gives to patients and staff. The benefit derived from the lower radiation dose can be quantified in monetary terms in accordance with procedures recommended by the International Commission on Radiological Protection (ICRP). These procedures are used internationally in the nuclear industry to establish the cost-benefit relation for the justification of expenditure to reduce radiation dose to the population. This is in accord with the general proposition that governments should reduce radiation exposure to the public to 'as low as is reasonably achievable' (the ALARA principle). ALARA has been adopted by the National Health and Medical Research Council as a code of practice for Australia. Appendix B shows that if this approach is adopted and applied to the use of the cyclotron-produced radioisotope iodine-123 in place of the reactor-produced radioisotope iodine-131, an annual expenditure of $6.6 million would be justified. On this basis alone, the installation of a cyclotron to produce iodine-123 is cost-effective.

Economic Benefit

Confidence exists, in the terms described in Section 6, that although an Australian cyclotron cannot be commercially profitable and 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 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 costing $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 Benefit

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, perhaps including a commercial enterprise for the production of radio-immunoassay kits for which the present market is some $10 million.

Future Potential Benefits

Associated with the national cyclotron, a National Institute for Nuclear Medicine could be established as a national centre for research into the use of short-lived radioisotopes and cyclotron beams, evaluation of new in-vivo techniques (such as PET and NMR) and training in all aspects of nuclear medicine - see Appendix C. It would also involve establishing a cooperative arrangement between the AAEC and hospitals and medical schools in all States to ensure nationwide access to the facilities by clinical research workers, in accordance with ASTEC principles governing the utilisation of costly national facilities. The additional cost could vary between 2 and 8 million dollars, depending on the facilities to be provided.

8. ROLE OF THE AUSTRALIAN AEC

The AAEC, through its Isotope Division, established a radioisotope advisory service in 1956 and commenced the production of radioisotopes, primarily for industrial application, in 1960. This activity, however, was low key 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 advanced 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 advanced 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.

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 directly or indirectly have been carried out. In mid-1970, the AAEC approved in principle the setting up of a cyclotron facility and its incorporation into a five year program at Lucas Heights. The ensuing working committee consisting of AAEC and Department of Health staff concluded inter alia that: 'it is unlikely that at present projections of demand the provision and operation of a cyclotron could be regarded as a commercial enterprise in Australia. The prime justification is to provide a national service to meet a medical need'. In October 1970 the Radioisotope (Reference) Sub-Committee of the National Health and Medical Research Council in a special meeting suggested to the Council that it, 'recommend steps be taken to provide for the Australian production of short-lived cyclotron-produced radioisotopes for use in medical diagnosis in Australia'. However, there was no progress on this initiative at that time.

Commission staff had further discussions in 1979 with medical practitioners and reached the view that any further initiative for the establishment of a medical cyclotron facility should rest with the medical profession, but that the AAEC would be willing to cooperate in any such undertaking. Also, it was considered that it would probably be appropriate for such a facility to be located at a major hospital where the cyclotron could be used for clinical research and treatment, as well as for the production of neutron-deficient isotopes.

At about the same time an ad-hoc advisory committee provided a report for the AAEC on the formation of an Australian Institute of Nuclear and Radiation Medicine. This report was later provided to the NERDDC Committee reviewing the AAEC's research programs and to the Ministers for Health, and National Development and Energy in 1979. The report concluded that a national institute should be set up along the lines of the Australian Institute of Nuclear Science and Engineering with a core membership representing interested parties within Australia.

Recently the AAEC completely revised its program and decided to place more emphasis on the medical applications of radiation and radioisotopes in the following terms:

> Radioisotope Production : 'The Commission also supports the continued indigenous production of as wide a range of radioisotopes and radiation services as possible. This activity, together with other commercial operations, has been combined within the Commercial Products Unit. The

Commission is proposing the acquisition of a cyclotron facility to enable a much wider range of radioisotopes to be available in Australia, and to open new fields of nuclear medicine research in which the AAEC would have a key role'.

Nuclear Medicine : 'As the only indigenous source of radioisotopes the AAEC should expand research to support and complement its radiopharmaceutical production. This will include synthesis of new radiopharmaceuticals for diagnostic and therapeutic medicine using reactor-generated and, if possible, cyclotron-generated radioisotopes, investigations of new and improved methods of manufacture and quality control, studies of possible drug interactions, radiation biology and radiation dose rate effects in radiotherapy, and research in collaboration with the medical fraternity into novel methods of radioisotope diagnosis and therapy. Of particular interest is nuclear magnetic resonance, in which the nuclear properties of non-radioactive isotopes can be used to study biochemical and physiological processes, as well as the imaging of structure'.

It is in this context of a 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 in radioisotope production and distribution.

Further, the Commission would wish to explore with relevant medical and health bodies the benefits of establishing a National Institute of Nuclear Medicine in association with the cyclotron as described in Appendix C. If such an Institute were to be established along the lines of the Australian Institute of Nuclear Science and Engineering (AINSE), the Commission would be an appropriate host organisation, in ASTEC terms, for its management.

9. 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.

Rather, it is considered highly desirable to have the flexibility to make maximum use of the cyclotron for advanced medical studies and training as mentioned in Sections 7 and 8, and dealt with in more detail in Appendix C.

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

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

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

(iii) within a reasonable distance (less than one hour) of Sydney Airport and Lucas Heights, to take advantage of the special nuclear and high technology skills of the AAEC and their existing complementary production and distribution service based on reactor products.

Following discussions between the AAEC and the Royal Prince Alfred Hospital (RPAH) which is associated with the University of Sydney the Chairman of RPAH has indicated agreement in principle to provide space for the cyclotron installation should the Government approve the proposal.

10. 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 D 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 R 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.

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APPENDIX A. LIST OF CYCLOTRONS USED FOR MEDICAL PURPOSES

Country	Installed (Recon-structed)	Location	Maker Model No. (or diam. in cm.)	Maximum Beam Energy ^1H unless stated (MeV)	External Beam Current (μA)	Used for isotope production D=dedicated	Wholly or primarily used for biomedical applications	Partly used for biomedical applications	PET install-ation (√)=on order
Belgium	1970	Univ. Louvain	CGR930S	95	20	√	-	√	√
	1973(82)	Univ. Liege	CGR520	21	30	√	-	√	√
	1977(81)	Univ. Ghent	CGR520	24	25-50	√	-	√	(√)
	1979	IRE Fleurus	CGR930	95	.	D	-	-	-
	1979	Univ. Brussels	CGR560	40	100	√	-	-	-
Brazil	1974	IEN, Rio	TCC/CV28	24	30	√	-	-	-
	1983	IPEN, Sao Paulo	TCC/CV28	24	30	√	-	-	-
Canada	1983	Triumf, Univ. Brit. Columbia, AECL	TCC/CP42	42	200	√	√	-	√
Czechoslovakia	1976	Rez	self-made	-	-	-	-	√	-
Finland	-	Tampere Hospital	USSR(110cm)	-	-	√	√	-	-
	1974	Abo Academy, Turku	USSR(103cm)	20	-	√	-	√	(√)
	1974	Uni. Jyvaskyla	Scand. MC20	20	10	-	-	√	-
France	1964	Villeurbanne	Philips	28(^2H)	15	√	-	√	-
	1965	INS, Grenoble	CGR 930	60	-	√	-	-	-
	1971	Orsay Hospital	CGR520	21	50	√	√	-	√
	1972(80)	CNRS, Orleans	CGR680	38	100	√	-	√	√
	1980	CEA, Saclay	CGR560	40	100	D	-	-	-
FRG	1964	Karlsruhe	AEG(225cm)	26	20	√	-	√	-
	1968	Julich	(330cm)	-	-	√	-	-	√
	1969	Bonn	AEG(200cm)	14	15	√	-	-	-
	1972	DKFZ, Heidelberg	AEG(109cm)	22	25	√	√	-	√

Country	Installed (Reconstructed)	Location	Maker Model No. (or diam. in cm.)	Maximum Beam Energy ^1H unless stated (MeV)	External Beam Current (µA)	Used for isotope production D=dedicated	Wholly or primarily used for biomedical applications	Partly used for biomedical applications	PET installation (√)=on order
FRG(cont.)	1975	Essen	TCC/CV28	24	50	√	√	-	(√)
	1976	Julich	TCC/CV28	24	50	√	-	√	√
	1977	Hanover	Scand. MC35	36	40	√	√	-	√
	1982	Karlsruhe	TCC/CP42(H^-)	42	200	√	-	√	-
GDR	1958	Dresden	USSR(U-120)	7	50	√	-	√	-
India	1981	BARC, Calcutta	224cm	50	•	√	-	-	-
Italy	1965	Milan Instit.	166cm	45	5	√	-	√	-
	1980	Pisa	CGR325	15	50	√	-	√	(√)
	1983	San Raffaele Hosp. Milan	Scan. MC40	40	65	√	-	√	-
Japan	1966	IPCR, Saitama	(160cm)	20	20	√	-	√	-
	1973	Univ. Tokyo	TCC/CS30	26	40	√	√	-	-
	1974	Nihon Medi-Physics	TCC/CS30	26	40	D	-	-	-
	1974	NIRS, Chiba	CGR930	70	15	√	√	-	√
	1977	Tohoku Univ.	CGR680	40	50	√	-	√	√
	1981	Nihon Medi-Physics	TCC/CS30	26	40	D	-	-	-
	1982	Kyoto	CGR325	15	50	√	-	√	√
	1984	Mallinckrodt, Tokyo	Scand. MC40	40	65	D	-	-	-
ROK	1984	Seoul	Scand.MC50 PF	50	70	√	√	-	√
Netherlands	1964	Petten	Philips(140cm)	30	•	D	-	-	-
	1965	Amsterdam	Philips(140cm)	28	20	√	-	√	√
	1968	Eindhoven	Philips(130cm)	30	50	√	-	√	-
	1970	Groningen	Philips(280cm)	65	15	√	-	√	(√)

(Continued)

Country	Installed (Recon-structed)	Location	Maker Model No. (or diam. in cm.)	Maximum Beam Energy ^1H unless stated (MeV)	External Beam Current (μA)	Used for isotope production D=dedicated	Wholly or primarily used for biomedical applications	Partly used for biomedical applications	PET installation (✓)=on order
Saudi Arabia	1982	Riyadh	TCC/CS30	26	60	✓	✓	–	✓
S. Africa	1958	CSIR, Pretoria	(112cm)	14	60	✓	–	✓	–
Sweden	1982	Karolinska Hosp., Stockholm	Scand. MC16	17	50	–	–	✓	✓
	1984	Uppsala	(230cm)	200	•	✓	–	✓	✓
Switzerland	1974	Wurenlingen	Philips(250)	75	150	✓	–	–	–
	1984	Wurenlingen		72	2000	✓	–	✓	✓
UK	1955	Hammersmith Hosp.	self-made	8	100	✓	✓	–	✓
	1965(75)	Amersham	(140cm)	•	•	D	–	–	–
	1966	Harwell	(178cm)	2-60	30	✓	–	✓	–
	1976	Edinburgh Hosp.	TCC/CS30	$15(^2H)$	70	✓	✓	–	–
	1982	Amersham	TCC/CP42	42	200	D	–	–	–
	1983	Clatterbridge Hosp.	Scand. MC60	60	50	•	✓	–	✓
	1985	Hammersmith Hosp.	Scand. MC40	40	65	–	✓	–	(✓)
USA		See Separate List							
USSR	–	Obninsk	(110cm)	•	•	✓	–	✓	–
Yugoslavia	1962	Ruder Boskovic, Zagreb	self-made	8	•	✓	–	✓	–

(Continued)

Country	Installed (Recon-structed)	Location	Maker Model No. (or diam. in cm.)	Maximum Beam Energy ^1H unless stated (MeV)	External Beam Current (μA)	Used for isotope production D=dedicated	Wholly or primarily used for biomedical applications	Partly used for biomedical applications	PET installation (√)=on order
U.S.A.	1951	Univ. Wash., Seattle	•	•	•	•	√	–	•
	1952(74)	Argonne N.L. Chicago	(152cm)	•	•	√	–	√	–
	1963(77)	ORNL, Tenn.	(193cm)	75	•	√	–	√	√
	1965	Wash. Uni. Med. School	Allis-Chalmers	•	•	•	–	√	–
	1965	Mass. Gen. Hospital	Allis-Chalmers	6(^2H)	75	√	√	–	√
	1966	Univ. of California, Davis	(193cm)	67	30	√	–	√	–
	1967	Sloane-Kettering, New York.	TCC/CS15	15	30	√	√	–	√
	1969	Argonne Cancer Res. Hospital, Chicago	TCC/CS15	15	30	√	√	–	√
	1971	UCLA, Los Angeles	TCC/CS22	22	50	D	–	–	–
	1971	New Engl. Nucl, Boston	TCC/CS22	22	50	D	–	–	–
	1971	Medi-Physics, Berkeley	TCC/CS22	22	50	D	–	–	–
	1972	Cleveland Clinic/NASA	(175cm)	45	20	√	–	√	–
	1973	Mediphysics, New Jersey	TCC/CS22	22	50	D	–	–	–
	1973	Mt. Sinai Hosp., Miami	TCC/CS30	27	20	√	√	–	√
	1976	New Engl. Nuc, Boston	TCC/CS30	27	20	D	–	–	–
	1977	Wash. Uni. Med. School	TCC/CS15	15	30	√	√	–	√
	1977	UCLA, Los Angeles	TCC/CS22	22	50	√	√	–	√
	1978	New Engl. Nucl, Boston	TCC/CS30	27	20	D	–	–	–
	1979	Mediphysics, Illinois	Scand. MC40	40	65	D	–	–	–

(Continued)

Country	Installed (Recon-structed)	Location	Maker Model No. (or diam. in cm.)	Maximum Beam Energy ^1H unless stated (MeV)	External Beam Current (µA)	Used for isotope production D=dedicated	Wholly or primarily used for biomedical applications	Partly used for biomedical applications	PET install-ation (✓)=on order
USA (cont.)	1980	New Engl. Nucl, Boston	TCC/CS30	27	20	D	–	–	–
	1981	Radpharm, San Francisco	TCC/CS30	27	20	D	–	–	–
	1981	Mallinckrodt, Missouri	TCC/CS30	27	20	D	–	–	–
	1982	Univ. of Michigan	TCC/CS30	27	20	✓	•	•	✓
	1982	M.D. Anderson, Houston	TCC/CP42	42	200	✓	✓	–	(✓)
	1982	Mallinckrodt, Missouri	TCC/CP42	42	200	D	–	–	–
	1982	Mediphysics, Illinois	Scand. MC40	40	65	D	–	–	–
	1982	John Hopkins Hosp., Baltimore	Scand. MC16	17	50	•	•	•	✓
	1983	Univ. of Texas, Houston	Scand. MC40	40	65	–	✓	–	(✓)
	1983	Bethesda, Maryland	TCC/CV46	•	•	✓	–	✓	(✓)
	1983	Univ. Wash., Seattle	Scand. MC50	50	50	–	✓	–	(✓)
	1984	Mallinckrodt, Missouri	Scand. MC40	40	65	D	–	–	–
	1984	UCLA, Veterans Hosp.	TCC/CP45	•	•	✓	✓	–	(✓)
	1984	Univ. of Pennsylvania	JSW	30	•	✓	•	•	(✓)
	1985	Univ. Hosp. of Cleveland	Scand. MC16F	17	50	•	•	•	•
	1987	Mediphysics, Illinois	CGR 930	70	40	D	–	–	–

APPENDIX B. FINANCIAL BENEFIT ATTRIBUTED TO REDUCED RADIATION EXPOSURE

To determine the state of a patient's thyroid the Australian nuclear physician must choose between two reactor-produced radioisotopes ^{131}I and ^{99m}Tc, neither of which is ideal:

> ^{131}I - Provides a complete diagnosis of the functioning of the gland at the expense of excessive radiation exposure.
>
> ^{99m}Tc - Provides partial diagnostic information only but radiation exposure is greatly reduced.

Approximately 20% of Australian physicians in nuclear medicine opt for ^{131}I; the other 80% employ a combination of techniques utilising both ^{131}I and ^{99m}Tc.

If cyclotron-produced ^{123}I were available however, the ideal goals of a full diagnostic picture at the expense of low radiation exposure could be achieved.

The International Commission on Radiological Protection (ICRP) has considered the optimisation of radiation protection and has developed a rationale and methodology to establish what is reasonably achievable in the control of radiation exposures. These procedures are based on a cost-benefit analysis which assumes that all the factors involved can be expressed in monetary terms.

> The 'as low as reasonably achievable' philosophy (ALARA) is a corner stone in the recommendations of the ICRP on radiation protection. Together, with the cost-benefit methodology it has been fully endorsed by the National Health and Medical Research Council in the 1981 publication 'Recommended radiation protection standards for individuals exposed to ionising radiation'. The optimisation of radiation protection procedures through the application of the ALARA principle is now almost mandatory in many overseas government establishments and in Australia.

Using this technique it is possible to derive the costs associated with the replacement of ^{131}I by ^{123}I and thereby the expenditure justified in making the replacement.

Radiation Exposure; ^{131}I versus ^{123}I

In techniques where a radioactive substance is internally administered, the patient is necessarily exposed to potentially harmful radiation. The extent of the radiation exposure depends upon:

- How much of the radionuclide is administered.
- The type and quality of the radiation emitted by the radionuclide.
- How long the radionuclide remains within the patient.
- The pattern of distribution within the patient.

The effectiveness of instruments used to plot the distribution is also influenced by the radioactive properties of the substance administered. Since most imaging instruments use only a thin, thallium activated, sodium iodide crystal as the detector, detection efficiency tends to fall away with increasing photon energy. Determination of the origin in space of a photon detected by the NaI (Tl) crystal requires a lead collimator placed in front of the detector. The design of this device is governed by the energy of the emitted photons; efficient collimation is lost as the photon energy is increased.

The actual calculations of the comparative radiation exposures for ^{131}I and ^{123}I are complex and, in the case of ^{123}I, it is complicated further by production considerations and the time dependent pattern of radionuclide impurities. A conservative estimate of the radiation dose to the thyroid for each radioisotope is shown in the Table B1, for three types of thyroid disorders.

TABLE B1

Radionuclide	Administered Activity (μCi)	Total Dose (rads)		
		Euthyroid	Hyperthyroid	Hypothyroid
^{123}I	100	3.5	8.4	1.5
^{131}I	25	52.5	92.5	21
$\Delta(^{131}I-^{123}I)$ Radiation Dose		49.0	84.1	19.5

Using the ICRP methodology, the equivalent monetary value attached to replacing ^{131}I by ^{123}I in thyroid studies is equal to :

$$Np\,[(Xr)_{131} - (Xr)_{123}] + \alpha\omega Np\,[(Hp)_{131} - (Hp)_{123}]$$

where: Np = Total number of patients per year
$(Xr)_{123}$ = \$ Cost of a unit dose of ^{123}I
$(Xr)_{131}$ = \$ Cost of a unit dose of ^{131}I
$(Hp)_{123}$ = Radiation exposure resulting from a unit dose of ^{123}I
$(Hp)_{131}$ = Radiation exposure resulting from a unit dose of ^{131}I
α = The monetary value assigned to the unit of effective (whole body) radiation exposure
ω = Weighting factor to take account of radiation sensitivity of an organ relative to that for whole body irradiation.

The numerical values for these terms are:

Np = 11,000 euthyroid patients + 7,000 hyperthyroid patients
$(Xr)_{123}$ = \$9.2/100 μCi;
$(Xr)_{131}$ = \$2.6/25 μCi
$(Hp)_{123}$ and $(Hp)_{131}$ - values are given in Table B1
α = \$200/rad
ω = 0.03 for the thyroid.

Substitution of these values into the ICRP formula shows that a change from ^{131}I to ^{123}I in Australia represents a monetary benefit in excess of \$6.6M/year.

It is this amount that provides the upper limit of expenditure for the reduction in patient dose if medical practices had to observe the radiation protection standards. Therefore, judged on internationally accepted radiation protection criteria, the installation of the cyclotron is certainly cost effective.

APPENDIX C. A NATIONAL INSTITUTE OF NUCLEAR MEDICINE - A POSSIBLE FUTURE DEVELOPMENT

Introduction

Under the present proposal the cyclotron is to be used for producing those cyclotron radioisotopes which have a half-life sufficient for them to be distributed effectively to all hospitals in Australia and the near geographic region. Although this overcomes a basic deficiency in the provision of health care by nuclear physicians, it does not fully exploit the potential of a national medical cyclotron.

A desirable development would be to establish a National Institute of Nuclear Medicine in association with the cyclotron, to act as the national centre for research into the use of short-lived radioisotopes and cyclotron beams, evaluation of new in-vivo techniques (such as positron-emission tomography (PET) and nuclear magnetic resonance (NMR)) and training in all aspects of nuclear medicine.

A suitable model is the Australian Institute of Nuclear Science and Engineering, at Lucas Heights, a cooperative venture between the AAEC, all Australian universities and the CSIRO, which was specifically designed to make the unique facilities at Lucas Heights available to the community. Such a utilisation of resources makes good economic sense and is consistent with the ASTEC principles governing costly national facilities.

New Medical Imaging Techniques - PET and NMR

Of particular interest is the development over the last 10 years of positron-emission tomography which measures many biochemical and physiological functions by using compounds labelled with ultra short-lived, positron-emitting radioisotopes (^{11}C, ^{13}N, ^{15}O and ^{18}F) made in a cyclotron.

Because a positron is an anti-electron, it combines with an electron and the masses of the electron and positron annihilate to form two 511 keV photons that are emitted 180 degrees apart. These photons easily penetrate the body and can be recorded by external radiation detectors. By using an array of detectors around the part of the body to be studied, electronic circuitry and a computer (constituting a positron-emission tomograph) the points of emission of the photons can be calculated and a picture displayed on a screen in a similar way to those from the well-known CT X-ray scanner. However, the resulting information is an indication of function rather than anatomical location as in CT scanning and it enables kinetic studies to be made with high sensitivity and precise location. In particular, it has already revolutionised the study of the functioning of the brain and the technique is still in an early stage of development.

For research and clinical use PET is 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 angina;
- 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.

Because the main positron-emitting radioisotopes of biological interest are ultra-short-lived, PET facilities must be located with the cyclotron and also within a large teaching hospital to ensure access to patients and to medical and academic specialities.

A logical next step 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.'

Thirty-four PET centres exist in Europe, North America and Japan and another 15 are planned, making a total of 49. Some are part of an imaging centre including NMR scanning.

Cancer Therapy

It is claimed that the beams available from cyclotrons (including neutron beams) are more effective than other forms of radiation therapy for some forms of cancer. Indeed, a number of medical cyclotrons (e.g. in the UK and USA) are used primarily for this purpose. This option would be available to Australia in association with the cyclotron.

Benefits

The concept of a National Institute for Nuclear Medicine in association with the medical cyclotron offers the following benefits:

(a) The Institute could be a national research centre of international repute, with nationwide access by clinicians and research workers, for the study of fundamental biochemical and physiological processes vital to a proper understanding of the pathophysiology of disease (and perhaps for the study of neutron beams for cancer therapy).

(b) The Institute could have an important training function for physicians, chemists, physicists and technologists employed in nuclear medicine throughout Australia and also New Zealand and South East Asia.

(c) The Institute could evaluate the new expensive technologies, e.g. PET and NMR, develop operational and training procedures, and promote standards and the national dissemination of information. These benefits, combined with nationwide access to the facility, should allow better control of expenditure on high technology health care by avoiding unnecessary proliferation of techniques and facilities and by developing optimal guidelines for expenditure under the national medical health scheme.

Costs

The major capital costs envisaged to cover the equipment, its accommodation and associated facilities are:

PET camera with associated hot-cells	$3 million
NMR scanner	$2 million
Isocentric neutron beam therapy head and shielded room for cancer treatment	$3 million

Additional accommodation would also be needed to house the permanent core staff and the visiting clinical research workers. This would depend on the facilities provided.

If the Institute were modelled on AINSE, the overall operating costs could be of the order of $1 million annually (depending on the facilities) of which a portion would be contributed by the participating members and the remainder by the Federal Government. The funds would be used to support a small permanent staff and to enable specialists and research workers, sponsored by the members, to work at the Institute as required.

Management

As for AINSE, the AAEC could be the host organisation with the operations controlled by a council of members' representatives primarily to ensure nationwide access to and effective use of the expensive research facilities. The AINSE concept has been very successful for the effective utilisation of the specialised facilities at Lucas Heights and a similar medical institute is strongly recommended for consideration.

APPENDIX D. LETTERS IN SUPPORT OF A NATIONAL MEDICAL CYCLOTRON

[COPY AS DICTATED BY DR BUTTFIELD 29/3/84]

IHB 15th June, 1983

Dr. N. Blewett,
Minister for Health,
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 NSW 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 interest of patients with a range of diseases requiring investigation, including cancer, coronary artery disease, stroke and severe trauma, and in the national interest. To support the development of a national cyclotron facility we feel that the following major points of principle are worth consideration in any deliberations of this subject:

(a) There is considerable public benefit from the development of such a facility, not only to the patients that may be treated or for the money saved by the tax payer, 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 run and may become a significant foreign income earner in the long run.

(c) The radioactive materials made by these machines have an established place in current medical practices 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.

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 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 you see fit.

Yours sincerely,

I.H. BUTTFIELD
President

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 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 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 vanderSchaaf
Agatha A van der Schaaf

Michael F Quinlan
(Chairman)

J Harvey Turner

Vincent Antico

Ivor Surveyor
(Secretary)

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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Yours sincerely,

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