THE POTENTIAL AND APPLICATIONS OF CYCLOTRONS IN BIOMEDICAL FIELDS

M. A. Chaudhri

School of Physics, University of Melbourne, Parkville 3052, Australia and University of Islamabad, Pakistan

Abstract

Applications of cyclotrons in biomedical fields like radioisotope production; activation and reaction analysis with charged particles and neutrons both of in-vitro and in vivo types; production of fast neutron beams for therapy, etc. are described. Production yields of various isotopes in use through different nuclear reactions have been compared with the yields calculated using experimentally measured or empirically constructed excitation functions. Detection sensitivities of various elements in tissue through activation induced by protons, deuterons and alphas of different energies are presented. Fast neutron beams produced from Be, D_2, D_2O and ^7Li targets with different sized and priced cyclotrons are critically compared. It is suggested that a Li-7, deuteron or even a heavy water target would produce a more penetrant neutron beam with relatively smaller cyclotrons than the commonly used Be target.

1. Introduction

Interest in the medical applications of cyclotrons has been increasing steadily over the past few years. Many institutions around the world have medical cyclotrons operating or under installation/order. Until the early sixties the Hammersmith Cyclotron was the only cyclotron fully devoted to medical applications. However, this number grew to 4 in 1967, to 14 in 1974 and could well reach 20 before the year 1975 is out. A list of various medical cyclotrons in different parts of the world is given in Table I.

There are also 5 commercial cyclotrons which are producing radiopharmaceuticals and engaged in market oriented applications. Besides, there are a number of national laboratories or universities where cyclotrons are, at least partly, used for isotope production, activation analysis, neutron therapy etc. Lists of these two categories of cyclotron installations are given in Tables II and III respectively. Some of the cyclotrons may have inadvertently been left out from this listing.

In Table IV energy specifications of the commercially available cyclotrons are summarised. Variable energy machines are more expensive than the fixed-energy ones (the difference between CV-28 and CS-30 is around \$180,000 [1]) but they are more flexible too.

2. Applications

Medical applications of cyclotrons lie mainly in the fields of isotope production, activation analysis and production of fast neutrons for therapy. Other medical applications like proton and heavy particle therapy; meson therapy, etc. using bigger machines are being discussed in other contributions at this Conference[2,3]) and would, therefore, not be included in this paper.

Table I Medical Cyclotrons

Location	Manufacturer	Installation
Hammersmith Hospital, London, U.K.	Medical Research Council	1955
Mallinckrodt Institute of Radiology, St.Louis,USA	Allis-Chalmers	1965
Massachusetts General Hospital, Boston, USA	Allis-Chalmers	1967
Sloan-Kettering Institute for Cancer Research, USA	Cyclotron Corp. (CS-15)	1967
Argonne Cancer Research Hospital, Chicago, USA	Cyclotron Corp. (CS-15)	1969
Service Hospitalier Frédéric Joliot, Orsay, France	Thompson-CSF (Compact)	1971
University of California, Los Angeles, USA	Cyclotron Corp. (CS-22)	1971
Institut fur Nuklearmedizin, Heidelberg, Germany	A.E.G.(Compact)	1972
Mount Sinai Hospital, Miami, Florida, USA	Cyclotron Corp. (CS-22)	1972
Instituto de Engenharia Nuclear, Rio De Janeiro, Brazil	Cyclotron Corp. (CV-28)	1973
Institute of Medical Sciences, University of Tokyo, Tokyo, Japan	Cyclotron Corp. (CS-30)	1973
Institute of Radiological Sciences, Chiba, Japan	Thompson-CSF(70)	1974
University of Liège, Belgium	Thompson-CSF	1974
Klinikum, Essen, Germany	Cyclotron Corp. (CV-28)	1975
Medizinische Hochschule, Germany	Scanditronix (MC-20)	1975
Kernforschungsanlage, Jülich, Germany	Cyclotron Corp. (CV-28)	1975
Western General Hospital, Edinburgh	Cyclotron Corp. (CS-30)	1975

Table II Commercial Cyclotron Installations

Location	Cyclotron Manufacture	Installation
Philips-Duphar Ltd., Petten, Holland	Philips	1964
Radiochemical Centre, Amersham, U.K.	Philips	1966
New England Nuclear Corporation, USA	Cyclotron Corp. (Cs-22)	1970
Medi-Physics Inc., California, USA	Cyclotron Corp. (Cs-22)	1971
Medi-Physics Inc., California, USA	Cyclotron Corp. (Cs-22)	1972

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Table III Cyclotron Installations in National Laboratories and Universities where Medically Oriented Work is Carried Out

1. Argentina Atomic Energy Commission, Buenos Aires
2. Atomic Energy Research Establishment, Harwell, U.K.
3. University of Birmingham, U.K.
4. Brookhaven National Laboratory, N.Y., U.S.A.
5. Kernforschungszentrum, Karlsruhe, W. Germany
6. Kernforschungsanlage, Juelich, W. Germany
7. Lawrence Radiation Laboratory, Berkeley, U.S.A.
8. Max-Planck-Institut fuer Kernphysik, Heidelberg, W. Germany
9. Naval Research Laboratory, Washington D.C. U.S.A.
10. Oak Ridge National Laboratory, U.S.A.
11. Physikalisch-Technisch-Bundesanstalt, Braunschweig, W. Germany
12. Texas A and M University, College Station, U.S.A.
13. University of Milano, Italy
14. Université Catholique de Louvain, Belgium
15. Washington University, Seattle, U.S.A.
16. Zentral Institut fuer Kernforschung, Rossendorf, E. Germany

The calculated yields are for guide lines only in order to optimize the actual production and may be in error by as much as a factor of two in the case of empirically constructed excitation functions[5]). For comparison between the actually measured and calculated yields the saturation yields would have to be converted into yields at time 't' where 't' is the time for actual bombardment by using the factor $(1 - e^{-\lambda t})$.

Using cyclotron produced ^{11}C, ^{13}N, ^{15}O, ^{18}Fe and ^{123}I a number of organic compounds and pharmaceuticals have been labelled[7]) which offer a great diagnostic potential. Diagnostic applications of cyclotron produced isotopes and labelled compounds are being described in another contribution[8]) at this Conference.

Table IV Specifications of Commercially Available Medical Cyclotrons

		CS-22[1]	CS-30[1]	CV-28[1]	Actitron[2]	Th-CSF (70)[2]	MC-20[3]
Beam Energy	p	22	26	2 - 24	6 - 19	8 - 70	2.5 - 20
(MeV)	d	12	15	2 - 14	3 - 11	11 - 35	1.5 - 10
	^3He	31	39	5 - 36	3 - 28	18 - 93	3.0 - 27
	α	24	30	6 - 28	6 - 22	22 - 70	2.5 - 20

1. The Cyclotron Corporation. 2. Thompson-CSF 3. Scanditronix.

2.1 Production of Radioisotopes

Production of radioisotopes for diagnostic studies is by far the most well known medical application of cyclotrons, and most medical cyclotrons are busy producing a variety of isotopes for research and routine work in nuclear medicine and nuclear biology. Generally neutron-deficient, carrier free and shorter-lived isotopes, which cannot be produced in a reactor, are produced with cyclotrons. However, at the same time neutron enriched isotopes can also be produced with cyclotrons, if required, through reactions of the type (d,p), (^{3}He,p) (α,p) etc.

Cyclotron production of most of the isotopes in use has been summarised in Table V.

Thick-target yields at saturation of each isotope through different nuclear reactions has been calculated[4]) using experimentally measured (for ^{11}C, ^{13}N, ^{15}O, ^{18}F and ^{52}Fe) or empirically constructed excitation functions[5]) and the range-energy data[6]). In the calculations the isotopic abundance of the particular isotope contributing to the nuclear reaction has been taken into consideration. However, the matrix which slows down the incoming particle beam in the target is assumed to consist of the element taking part in the nuclear reaction only, which is true when elemental targets are being used rather than compound ones.

Table V Cyclotron Production of Isotopes

Isotope	Reaction	Energy (MeV)	Target	Production Yield μci/μAh (or concentration)	Ref.	Calculated yield at saturation[4] mCi/μA	Energy (MeV)
^{11}C	$^{11}B(p,n)$			- - - - - - -	---	405	11.5
	$^{10}B(d,n)$ + $^{11}B(d,2n)$	14	B_2O_3	5 mCi/min CO - 100 mCi per litre of H_2 carrier gas - 70 mCi per 35 ml of He CO_2 - 50 mCi in 35 ml of He	9	80	14
	$^{12}C(^3He,\alpha)$	15-18	CaC_2	2500	10	87 115	15 18
	$^{14}N(p,\alpha)$	15	$LiNH_2$	18 mCi/18 min of $H^{11}C\,N$	11	---	---
^{13}N	$^{12}C(d,n)$	14	Graphite	30 mCi/ml in gas form 100-300 μCi per ml in solution	12	300	14
	$^{14}N(^3He,\alpha)$	----	-----	---------	----	38	30
^{15}O	$^{14}N(d,n)$	5	4% O_2 in N_2	120 mCi of O_2 per litre of carrier gas 40 mCi/ml of H_2O	9	12.5	5
	$^{14}N(^3He,d)$	----	----	---------	----	26	17
^{18}F	$^{16}O(\alpha,pn)$	45 65	H_2O "	6200 19000	13 14	---	---
	$^{16}O(^3He,p)$	22	H_2O	6000	15	12	9.5
	$^{20}Ne(d,\alpha)$	8	Neon gas	10000	16	52 100	8 16
	$^{19}F(^3He,\alpha)$	----	----	---------	----	8	30
^{43}K	$^{40}Ar(\alpha,p)$	17	Argon	57	17	9	17
^{52}Fe	$^{50}Cr(\alpha,2n)$	30	natural Cr	3.3	18	.007	30
	$^{52}Cr(^3He,3n)$	45.5	"	50	19	----	---
		23		0.7	20	----	---
	$^{55}Mn(p,4n)$	65	MnO_2	160	21	----	---
^{62}Zn	$^{60}Ni(\alpha,2n)$	30	natural Ni	100	22	6	30
^{67}Ga	$^{65}Cu(\alpha,2n)$	30	natural Cu	160	23	8	30
	Zn(p,xn)	22	natural Zn	430	24	95	22
	Zn(d,xn)	8	"	100	25	2	8
	"	"	"	30	20		
^{77}Bi	$^{75}As(\alpha,2n)$	28	As_2O_5	160	26	25	28
^{81m}Kr		Decay product of ^{81}Rb					
^{85m}Kr	$^{84}Kr(d,p)$	15	Kr	790	27	60	15
^{81}Rb	$^{79}Br(\alpha,2n)$	30	NaBr	2000	28	18	30
		50	"	2900	29		

Isotope	Reaction	Energy (MeV)	Target	Production Yield µci/µAh (or concentration)	Ref.	Calculated yield at saturation[4] mCi/µA	Energy (MeV)
	$^{81}Br(^{3}He,n)$	22	NaBr	30	30	---	---
^{82m}Rb	$^{81}Br(^{3}He,2n)$	22	NaBr	80	30	---	---
^{83}Rb	$^{83}Kr(p,n)$	22	Natural Kr-gas	7	31	60	22
^{85}Sr	$^{85}Rb(d,2n)$	13	RbCl	15	32	70	13
^{87}Y	$^{85}Rb(\alpha,2n)$	32	RbCl	174	33	30	32
^{111}In	$^{109}Ag(\alpha,2n)$	30	natural Ag	200	34	9	30
	$Cd(p,xn)$	15	natural Cd	140	20	35	15
	$^{111}Cd(p,n)$	16	enriched ^{111}Cd	515	35	150	16
^{123}I	$^{121}Sb(\alpha,2n)$	25	natural Sb	150	36	3	25
		25-36	enriched ^{121}Sb	900	37	6-30	25-36
	$^{121}Sb(^{3}He,n)$	23	natural Sb	24	20	---	---
	$^{122}Te(d,n)$	6-9	enriched ^{122}Te	100	37	0.3	9
	$^{123}Te(p,n)$	15.5	enriched ^{123}Te	450	38	140	16
	$^{124}Te(p,2n)$	30	enriched ^{124}Te	40000	39	1300	30
^{123}Xe	$^{122}Te(\alpha,3n)$	46	enriched ^{122}Te	5000	40	---	---
	$^{123}Te(^{3}He,3n)$	30	enriched ^{123}Te	750	41	---	---
		42	gas flow powder enriched ^{123}Te				
^{127}Cs	$^{127}I(^{3}He,3n)$	22	NaI	500	43	---	---
^{129}Cs	$^{127}I(\alpha,2n)$	30	NaI	170	44	18	30
		35	"	300	45	30	35
		36	"	700	46	30	36
^{157}Dy	$^{159}Tb(p,3n)$	30	Terbium foil	23000	47	500	30
			$TbCl_3 \cdot 6H_2O$	2500	48	---	---

Isotope	Reaction	Energy (MeV)	Target	Production Yield μci/μAh (or concentration)	Ref.	Calculated yield at saturation mCi/μA	Energy (MeV)
	$^{155}Gd(\alpha,2n)$	30	Gd	80	49	3	30
^{197}Hg	^{197}Au (p,n)	12.5	Gold	14	50	2	12.5
^{197m}Hg	^{197}Au (p.n)	12.5	Gold	15	50	---	---
^{203}Pb	^{203}Tl (p.n)	15	Tl metal	50	51	1	15
	^{203}Tl (d,2n)	16	Tl_2O	100	9	6	16
^{204}Bi	^{206}Pb (p.3n)	32	Pb	2000	52	180	32
^{206}Bi	^{207}Pb (p.2n)	22	Pb	700	53	110	22
	^{206}Pb (d.2n)	16	Pb	30	9	6	16

2.2 Activation Analysis

Accelerated charged particles like protons, deuterons, ^3He and alphas from cyclotrons can be used for carrying out activations and/or reaction analysis in biological materials. Charged particle activation is of special value in the analysis of lighter elements and of some heavier elements like Fe, Pb etc., which would not produce any conveniently measurable activities through thermal neutron capture. By bombarding suitable thick targets (Be, Li etc.,) with charged particles from cyclotrons intense neutron beams (of the order 10^{12}-10^{13} n/sec/cm^2) ranging in energy from zero to a certain maximum can also be produced. These neutrons can be used for fast neutron activation or be thermalized by passing them through paraffin wax and used for slow neutron activation as well. By choosing the right thickness of paraffin (about 5cm for 16 MeV deuterons on thick Be) the resultant neutrons can be used for both slow and fast neutron activation simultaneously.

2.1.1. Charged particle activation and reaction analysis. Activation and reaction analysis using different charged particles from cyclotrons have great analytical potential with detection limits of the order of 1 p.p.m.- 1. p.p.b.and in some cases even lower are attainable. However, not much work has so far been carried out in bio-medical fields. This is probably due to the fact that preparation of sample material for charged particle activation is a lot more difficult than with neutrons due to the energy loss of the incident particles in the target and consequent heating and deteriation of the sample.

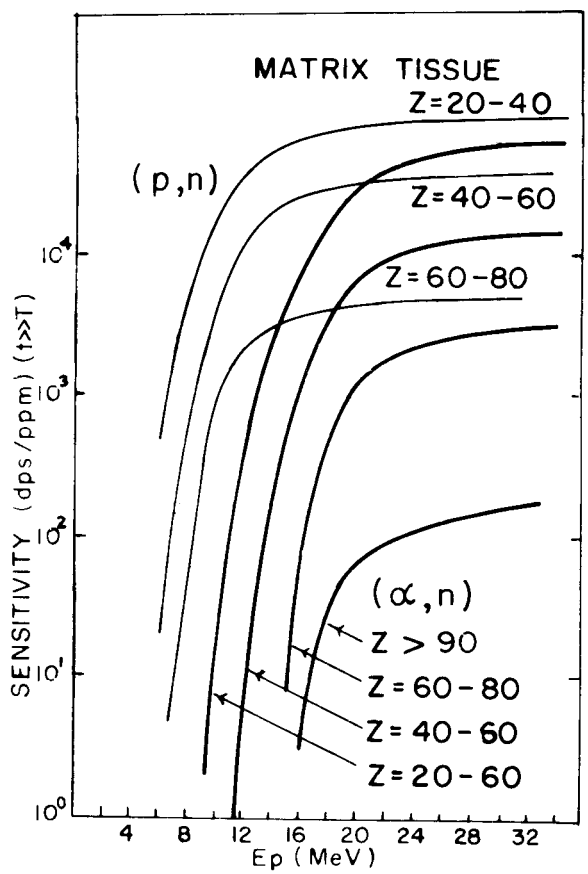

Fig.1. Thick target sensitivities of detection at saturation for elements with Z = 20 to Z >90 activated through (p.n) and α.n) reactions.

Detection sensitivities for various elements in tissue through activation by protons, deuterons and alphas of different energies [54]) are shown in figures 1 and 2. Due to space restrictions only curves for one particle-emission reactions have been included here. Reactions induced by ^{3}He have not been mentioned due to the non-availability of the relevant systematic excitation functions. It can be noticed that enough count rate would be there at concentrations of as low as 1 p.p.b. even at 1 μA of beam current. The data regarding elements with Z lower than 20 is in process and indicates that detection sensitivities are equally good and in some cases are even better.

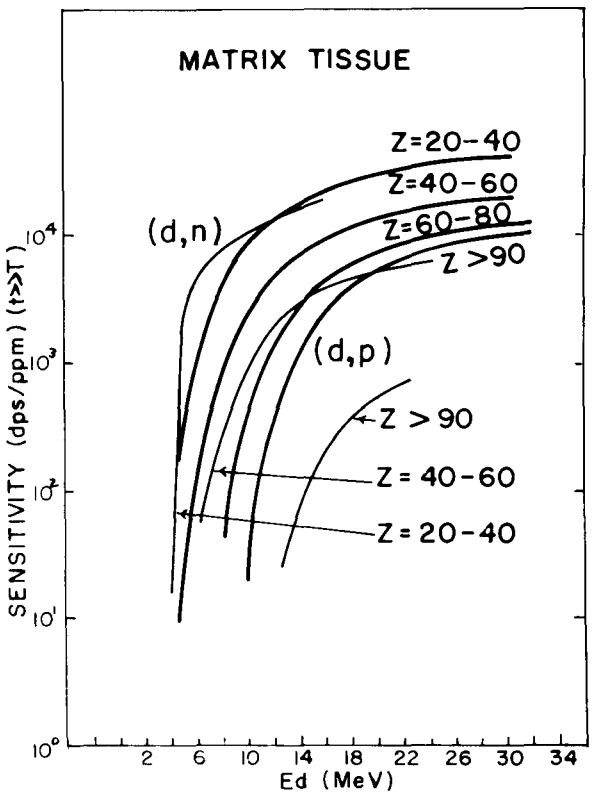

Fig.2. Thick target sensitivities of detection at saturation for elements with Z=20 to Z >90 activated through (d,n) reactions.

Back scattering of cyclotron alphas from thin biological samples for elemental analysis have been successfully used by Jolly and White [55]) who claim sensitivities for detecting heavy elements (A >16) in biological matter in atomic concentrations of 10^{-6} to 10^{-9}, Chaudhri and Collegues [56]) have used the prompt 6.13 MeV gammas from the reactions $^{19}F(p,\alpha\gamma)\,^{16}O$ for determining F concentrations in bones and other samples. They have further shown [57]) that with this technique concentration of lower than 1 p.p.b. should easily be obtainable. The possibility of nitrogen determination in biological meterials through(d,α) reaction has been demonstrated by Sundqvist and Co-workers[58]).

For elemental analysis through x-ray fluorescence 2-3 MeV protons from Van de Graaff Generators are ideally suited. However, cyclotron beams, preferably at lower energies can also be used for this purpose. The advantage of this technique being that almost all the elements heavier than Na can be analysed in one run. . Herman and Collegues [59]) have shown that with 6 MeV and even with 15 MeV alphas all the elements detected with 2-3 MeV protons can be determined, though the background is higher in the case of alphas.

2.2.2. Activation analysis with cyclotron produced neutrons. As already mentioned in this section, intense beams of neutrons can be produced by bombarding a thich Be-target with deuterons. At 16 MeV, the neutron flux is about 2.5 x 10^{13}/ sec/cm^2 for 100 μA beam current with an average energy ($\bar{E}$n) around 7 MeV. With larger cyclotrons both the neutron flux and ($\bar{E}$n) would be higher. This sort of neutron flux is a few orders of magnitude higher than obtained with most of the commercially available fast neutron generators and the target life much longer. Cyclotron neutrons can be used for carrying out fast neutron activation analysis of different elements and would provide better detection limits than the D-T generators in most cases. Induced activities of ^{11}C, ^{13}N and ^{15}O calculated in determining C,N and O in different samples with neutron produced by bombarding thick Be with deuterons of 100 μA intensity from different sized cyclotrons are given in Table V1.

TABLE V1.

Cyclotron Size (deuteron energy) MeV	Induced Activity at Saturation d.p.s./μg. C	N	O
15	----	20	----
20	----	80	1.5
24	4	400	6.5
40	600	2000	530
54	1400	5000	2000

It is evident from the tables that sub microgram quantities of C,N and O can be determined with cyclotron neutrons. The lowest detactable limit with the larger machines is in the nanogram region.

In spite of all the potential advantages of fast neutrons produced by cyclotrons, a limited amount of work has so far been carried out in bio-medical fields. Using the Hammersmith Cyclotron, Chaudhri and Batra determined the amount of Mg present in the dosimetric (Li F(TLD-100)[61]) and C to P ratio in small bone biopsies[62]). Concentration of Na, P, Cl and K have also been determined in needle biopsies of muscles [63]).

Due to the non destructive nature of neutron activation analysis, this technique has been successfully applied to in-vivo activations in estimation of total body Ca and to a lesser extent Na and Cl [64,65,66]).

For these measurements fast neutrons produced by cyclotrons are thermalized and activities induced through (n,γ) reactions determined. The total body dose required for Ca determination is only 0.2 rad and the accuracy and reproducibility of measurements are 5% and 2.3% respectively[66]). Attempts have also been made at Birmingham to determine total body N and the results from cadaveres indicate that only 0.1 rad would suffice in this case[67]).

Reactors and isotopic neutron sources have been used for part in-vivo activation analysis of I in thyroid and Ca, Na and Cl in superficial bones like tibia[68]). Similar measurements, especially for elements requiring fast neutrons for activation, should be quite feasable using cyclotron produced neutrons because of the greater flexibility of such beams.

3. Neutron production for therapy

Fundamentals of neutron radiobiology and neutron therapy are being discussed in another contribution at this conference[69]) and therefore, only the production of neutrons by cyclotrons is being dealt with in this section.

There are a number of institutions around the world who are carrying out (or planning to do so) experimental programmes in neutron therapy using a Be target in one form or another and bombarding it with deuterons for neutron production. There are two requirements on the neutron beams to be suitable for therapeutical application. Firstly, it should be capable of imparting a tissue dose-rate of 10-20 rads/min at a distance of 100-125cm from the target. Secondly, it should be able to penetrate a depth of about 10cm in tissue before its dose rate drops to about 50% of the original value. This requirement would put it at par with the depth-dose characteristics of a ^{60}Co-gamma source. Most of the cyclotrons in medical institutions are capable of producing many tens of μA of deuterons and therefore would produce quite sufficient dose-rate from Be targets. However, the mean energies of the neutron beams produced by smaller cyclotrons using a Be target fail to fulfill the penetration criterion and are therefore suitable for superficial tumors only. The larger cyclotrons capable of producing 30 MeV or higher energy deuterons do produce clinically acceptable neutron beams. These machines are more expensive than ordinary medical cyclotrons commercially available. It has been shown by Chaudhri and Co-workers[70-72]) that a much more improved neutron beam for therapy would be produced by a deuterium gas or even by a heavy water target than with a Be target under similar bombarding conditions. Technology for high-pressure deuterium gas and heavy water targets however, seems to be comparatively more difficult than for a Be target and this has probably deterred their introduction as neutron producing target for therapy. Chaudhri[73]) and Chaudhri and Co-workers[74]) have described simple, usable target designs for both deuterium gas and heavy water targets.

Recently Chaudhri and Coworkers[75])have suggested the use of a ^{7}Li-target as an excellent neutron producing source through the reaction ^{7}Li(p.n)^{7}Be. They have shown that using a thin Li target, a nice, clean neutron spectrum, with much lesser background can be obtained and at the same time the neutron beam remains intense enough to satisfy the dose criterion.

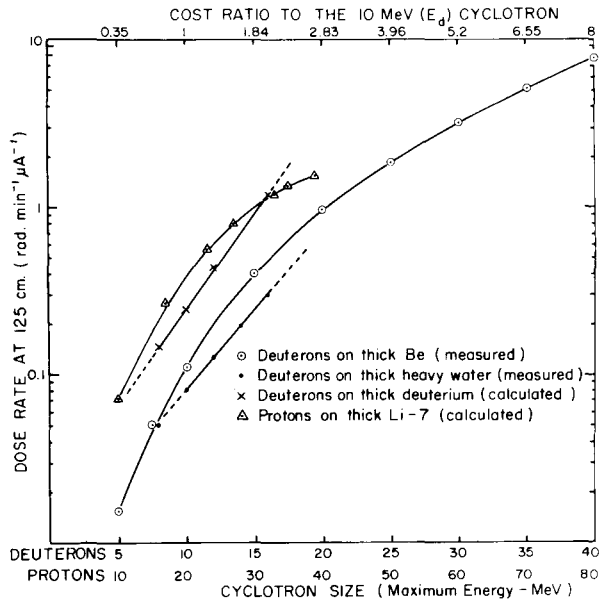

Fig.3. Forward direction neutron dose rates from various thick targets at different bombarding energies. (different sized cyclotrons).

Dose rates obtained at 125cm from thick targets of Be, D_2, D_2O and ^{7}Li in the forward direction produced under bombardment with charged particles from different sized machines are shown in in figure 3. The size of a cyclotron is classified by the maximum deuteron energy it can produce, proton energies obtained being double that for deuterons. Cost comparison of different sized cyclotrons with the 10 MeV machine is also given. It has been assumed that the cost of a cyclotron is determined mainly by the size of its magnet and therefore, would be proportional to $E^{3/2}$. The data for thick Be target is calculated using the empirically derived equation[76])

$$\text{Dose rate} = 1.24 \times 10^{-4} \times E_d^{2.99} \quad (1)$$

which is a fair representation of the experimental data up to 54 MeV. The data for D_2, D_2O and Li is taken from references (72,77 and 75)respectively. It is clear from the figure that both deuterium and Li targets would produce higher dose rates than either Be or D_2O whose dose out-puts are similar.

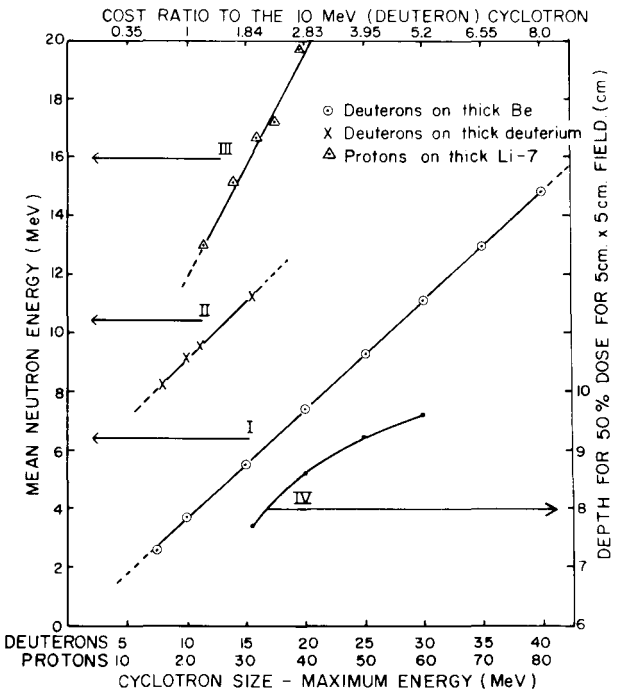

Fig.4. Mean energies in the forward directions from thick Be(I), D_2(II), and Li(III) as well as 50% dose-depths (IV) from thick Be at different bombarding energies.

Mean or average energies of neutron beams ($\bar{E}n$) produced in the forward directions from different sized cyclotrons with targets of D_2, D_2O and ^7Li are shown in figure 4. The data for $^2D_2$ and Li is from references (72) and (75) respectively. The values for thick Be targets are calculated using the empirical equation developed by Weaver and Colleagues [78]

$$\bar{E}n = 0.37 \times E_d \text{ MeV} \quad (2)$$

Equation (2) gives the mean energies of neutrons produced at 3.5° for deuteron energies of greater than 9 MeV and represents the experimental data within error limits up to 54 MeV deuterons. Also shown in the figure is the curve giving the depths in tissue equivalent liquid for a 5cm x 5cm field at which the neutrons produced by bombarding thick Be targets reduce to 50% of their dose at 0.5cm inside the liquid [79]. It can be seen from various curves in the diagram that in order to get a 50% dose-depth of 10cm a $\bar{E}n$ of about 10 - 11 MeV is required. To produce such a neutron beam from a Be target the 30 MeV deuterons are required which makes the cost of the corresponding machine about five times that of the 10 MeV deuteron cyclotron. Using a D_2 target even the 10 MeV machine would be sufficient and a lot cheaper. This means that in order to obtain better and cheaper neutron beams for therapy targets, other than Be, should be used in cyclotrons. Proton bombardment of ^7Li targets seems to be the best suggestion at present.

Neutron spectra from deuteron bombardment of thick targets of C,Cu,Mo,Ta and Au have been compared with that of a thick Be target at 16,33 and 50 MeV deuterons [80]. Though Be produces the most intense neutron beams, the spectra of neutrons and hence the corresponding average energies look fairly similar amongst the lighter elements at low energies and amongst almost all the elements studied at higher energies.

Neutron production with deuterons, of greater than a few MeV's would be accompanied by a great deal of break-up neutrons with much lesser energies in the neutron spectra irrespective of the targets used. This fact has clearly been demonstrated by Chaudhri and his Co-workers [70-72] by proving that no better neutron beam could be obtained by 16 MeV deuteron bombardment of tritium than with a deuterium target. Using proton beams for neutron production would avoid the presence of these low energy neutrons and therefore are preferable.

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