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CYCLOTRON PRODUCTION OF FAST NEUTRONS FOR THERAPY

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Abstract.- A brief review of the historical development of cyclotron production of neutrons for therapy, with special reference to our own contribution, is presented. Various nuclear reactions and target systems have been critically examined with regard to their suitability for cyclotrons of different sizes. A few current problems in this field, where the nuclear physics community can greatly contribute, are pointed out.

1. Introduction.- The interest in neutron therapy has been growing slowly but steadily over the past 10-12 years. While in the late sixties the Hammersmith Hospital, London, was the only institution seriously involved in this activity, there are now at least 16 centres around the world which are actively pursuing research and clinical programmes in the application of neutrons for treatment of cancer. These are located at Dresden, Tokyo, Essen, Edinburgh, London, Seattle, Chiba-Shi, Washington, Houston, Louvain, Batavia, Glasgow, Hamburg, Heidelberg, Manchester and Amsterdam. There are a few more institutions who are installing or planning to install neutron therapy facilities. Moreover, a number of other academic and research institutions are engaged in physical and radiobiological research connected with neutron therapy. However, in spite of all this, the true value of neutron therapy has yet to be properly assessed because of the technical difficulties involved in the production of suitable neutron beams for therapy.

From a therapy point of view, a suitable neutron source should be able to provide enough dose rate, at source to skin distance of about 100 cm, and have penetration at least equivalent to that of ^{60}Co gamma range. It is generally regarded that a treatment time per fraction of more than about 5 mins., or perhaps even 10 mins., is unacceptable from the patient's comfort point of view. A typical neutron dose delivered per fraction ranges between 100 - 200 cGy (rads.) Therefore, the neutron source should be able to deliver at least 12 to 20 rads/min. at the patient's position. Also, in order to achieve a penetration equivalent to that of ^{60}Co α-range, one requires a neutron beam with a mean energy of at least around 15 MeV. Of course, higher dose rates and penetration would be advantageous.

Out of the 16 institutions known to be carrying out neutron therapy, 10 (the first 10 in the list) use cyclotrons, one linear accelerator (Batavia), while the rest use D-T generators as sources of neutrons. The neutrons produced by D-T generators have an average energy of around 14 MeV, which is acceptable, but their flux is far from satisfactory. To increase the output of these generators, and increase the life of tritium targets (which is limited to only some tens or at the most a couple of hundred hours) is a major technical problem, although a number of groups around the world are working on it. With the cyclotron-produced neutrons, the problem is just the other way around. Most cyclotrons, including smaller ones, can produce adequate flux of neutrons, acceptable for therapy, by using proton or deuteron reactions on suitable targets. However, the penetration of cyclotron-neutrons is limited, unless large and expensive cyclotrons are used.

For more than a decade we have been examining the ways and means of improving the penetration of cyclotron neutrons, not by using bigger machines but by alternative nuclear reactions and target systems, and we have had a great deal of success in it. This alternative approach of improving the penetration, and hence the usefulness of cyclotron neutrons, its historical development and success, along with some general outstanding problems in this field, are points for discussion in this paper.

2. Neutron producing reactions.- Intense beams of fast neutrons for therapy are generally produced by bombarding thick targets of light elements (Li, Be, etc.) with accelerated charged particles from cyclotrons. These neutrons have a wide energy spectrum, ranging from zero to a certain maximum. The mean energy, and the intensity of such neutrons, depend upon the incident particle energy (and hence the cyclotron size and its cost), the neutron producing nuclear reaction and the target. Generally speaking, the higher the incident energy the greater is the intensity and the penetration of the neutron produced.

2a. Deuteron induced reactions.- The deuteron bombardment of a thick Be-target is the most commonly used nuclear reaction for producing therapy neutrons with a cyclotron or a similar high energy machine. All the institutions, with the exception of Fermi Laboratory (Batavia), are using this reaction. (The Fermi Laboratory uses protons incident upon Be). The intensity of neutrons produced with this reaction is adequate for therapy, even when smaller cyclotrons are used. The dose rate from the Be + d neutrons, at 100 cm from the target is given by [1]

$$K = 2.12 \times 10^{-4} \; E^{2.97} \text{ rads/min/}\mu\text{A}$$

This means that a small cyclotron capable of accelerating deuterons to 10 MeV, and having external beam currents of 100 μA (which are quite feasible in modern machines) could produce neutrons with dose rates of about 21 rads/min. at 100 cm distances.

The mean energy of neutrons from this reaction is,

however, not adequate except when larger and much more expensive machines are used, in spite of the fact that the Q-value of the reaction Be (d,n) is + 4.4 MeV. This is due to the low-energy neutrons which are coming from the Coulomb "break-up" of the deuterons : a phenomena which will be discussed later.

Some forward direction neutron spectra from thick Be-targets at different deuteron energies are compiled by Fowler.[2] These spectra show clearly that, as the deuteron energy increases, so does the mean energy of the neutron produced; the two being related by the following equation :

$$\bar{E}_n = 0.42E_d$$

This equation shows that, using a Be-target, it would not be possible to produce a usable neutron beam with cyclotrons of less than about 15-16 MeV deuteron energy, and even then it would be far from being ideal.

In the late sixties we started an extensive programme of examining alternative nuclear reactions and targets for producing neutrons with higher mean energies than produced by the d + Be reaction. On the basis of our calculations, we demonstrated as early as 1969 [3-5], for the first time ever, that deuterium could be a practical proposition as a neutron producing target in cyclotrons, and that it would produce neutrons with higher mean energies and intensities than those produced with a Be target under similar bombarding conditions. For example, a 10 MeV deuteron beam would produce neutrons with a mean energy of about 9 MeV from a deuterium target, which is higher than that of neutrons from 16 MeV deuterons on Be.[3-5] This indicates that even a small cyclotron, with a maximum deuteron energy of only 10 MeV, could produce a neutron beam comparable to that of the Hammersmith cyclotron in penetration, and higher in intensity.

The results of our calculations have since been verified both experimentally and theoretically, [6-9] and now there are a number of institutions who are using, or planning to use, deuterium gas as a neutron producing target in their cyclotrons. The use of a deuterium gas target is, however, technically more complex than using a thick Be target. Cells containing high pressure gas to act as thick targets, but still having thin entrance windows to minimize the energy loss by the incoming beam, have to be designed for long and reliable operation. In order to make this apparently difficult task easier, we suggested the use of a 20 cm long gas cell with only a few atmosphere of deuterium pressure in it.[5,10] We demonstrated by extensive calculations that by absorption of only a few MeV's from the incoming beam into the target, instead of completely stopping it one could still produce a therapeutically acceptable neutron beam.[10] For example, a 16 MeV deuteron beam would lose 2 or 3 MeV in the gas target with 3.19 or 5.26 atm. pressure respectively, and produce neutron dose rates of 36 and 63 rads/min at a distance of 100 cm from the target.[10] Also, it is a lot easier to construct a cell for holding 3 or 5 atm. of deuteron gas, rather than for 20 atm., which would be required to stop the 16 MeV beam completely.

It was also shown by us theoretically, [3-4] and experimentally,[11] that a heavy water target would produce a more penetrant neutron beam than a Be target at the same bombarding energies, and that reasonable neutron therapy programmes could be conducted with small cyclotrons (deuteron energy of around 10 MeV) using such a target.[12]

During our investigations we also calculated the neutron spectra and intensities from the deuteron bombardment of a thick tritium target at different incident energies. We found that the neutron intensity from a thick tritium target was almost identical to the neutrons from a deuteron target. However, what surprised us most was the result that, in spite of the difference in the Q-values of d + D and d + T reactions (3.8 and 17.6 MeV respectively), there was little difference between the average neutron energies from the two targets, especially at higher energies.[3-5] For example, the average neutron energies from thick deuterium and tritium targets, at deuteron energies of 8, 10, 12 and 16 MeV were 8.2, 9.1, 9.5 and 11.3 MeV (for D) and 14.8, 13.3, 12.6 and 12.3 MeV (for T) respectively.

The similarity between the neutron mean energies from the two targets is attributed to the role of (d,np) neutrons, which are produced by the break-up of the deuteron in the coulomb field of the target. The threshholds for this reaction from deuterium and tritium are 4.4 and 3.7 MeV respectively. Its cross-section increases rapidly with increasing deuteron energy. These neutrons have much lesser energy than the (d,n) neutrons and, due to their large number, would bring down the mean energy of the entire spectrum, irrespective of the Q-value of the (d,n) reaction. Based on this finding, we were able to point out categorically, for the first time ever, that tritium has no advantage (but some disadvantages) over deuterium as a neutron producing target in cyclotrons, especially at higher deuteron energies.[3-4]

It is also due to these break-up neutrons that the average energies of neutrons produced by thick Be and Li targets, 0.42 E_d and 0.44 E_d respectively, are very similar in spite of a large difference in the Q-values of the reactions Be (d,n) and ^{7}Li (d,n) (4.4 and 15.0 MeV respectively).[2] Moreover, this break-up phenomena also provides a possible explanation as to why the shapes of the neutron spectra from a number of targets, from Be to Au, appear to be similar, especially at higher deuteron energies.[13] This shows that at higher incident energies the neutron spectra from most of the elements, with the exception of very light ones like D and T, would be similar, irrespective of the Q-value of the reaction or the level structure in the daughter nucleus.

2b. Proton induced reactions.- In the early seventies, we started investigating proton induced reactions as possible sources of therapy neutrons, mainly for two reasons. Firstly, the available proton energy from a modern isochronous cyclotron is about twice that of the deuteron, and is therefore likely to yield neutrons with higher mean energies. Secondly, we presumed that the contribution of the "3-body-break-up" neutrons might not be as significant as in the case of (d,n) reactions.

Using the thin target ^{7}Li (p,n) neutron spectra of Jungerman et al,[14] and the available cross-section data, we empirically constructed the thick target neutron spectra of this reaction at different bombarding energies.[15] We were the first to suggest the use of a Li target for production of neutrons with

cyclotrons, and demonstrated for the first time ever (as far as we are aware) that a ^{7}Li target would produce neutrons with much higher mean energies when bombarded with protons from a cyclotron, than any reaction using deuterons from the same machine at similar beam currents.[15] We calculated that incident proton beams of 39, 35, 32, 28, 23, 17 and 10 MeV would produce, from a thick Li-7 target, neutrons with average energies of 19.7, 17.2, 16.7, 15.1, 13.0, 7.2 and 4.5 MeV respectively.[15] It is extremely pleasing to note that these average energies, which have been derived using our "crude" empirical method, are in good agreement with those measured by Lone et al,[16] and with his extrapolated data. The neutron intensities from this reaction, at all the incident energies, were also found to be adequate for therapy. We also showed that, by using a moderately thick (not stopping the beam completely) rather than a thick Li-7 target, one could further increase the mean neutron energy and obtain a much cleaner (fewer lower energy neutrons) neutron spectrum, and still retain adequate neutron intensity.[15] We verified this result experimentally using the Melbourne University cyclotron.[17]

Since our results were published, a number of groups around the world have also advocated the use of proton, instead of deuteron, induced reactions on Li and Be as suitable sources of therapy neutrons with cyclotrons, and have carried out extensive measurements on the intensity and spectra of these (p,n) neutrons.[18-24] Most of the experimental arrangements used by these authors have a neutron-energy threshhold of about 10 MeV (meaning that they could not measure neutrons of less than 10 MeV), with the exception of Graves et al,[22] who could measure neutrons of as low as 1.4 MeV, and it is quite likely that there are a lot of low energy neutrons which would not be observed by them experimentally.[20] Keeping in mind this limitation in the experiments, their results indicate that:[20]

1. Li and Be targets of equivalent thicknesses would produce neutron beams of almost similar characteristics (Li being slightly better), when bombarded with protons.

2. Protons from a cyclotron incident on a Be target would produce a more energetic, more penetrating, more skin sparing and a more intense neutron beam than that produced by the deuterons, from the same cyclotron, at the same currents, from a Be target.

The authors[20] advocate the use of a Be target, as it is easy to handle, has a high melting point, adequate heat conduction and is chemically inert. However, Li has its advantages too. It is more readily available, cheaper and less hazardous and more convenient to handle than Be. Due to its low melting point, it should be quite feasible to design a simple liquid-Li target for cyclotron use. Presently we are working on such a design.

As we pointed out by our calculations,[15] the experimental results also demonstrate that, using proton induced reactions on Li and Be, even small cyclotrons (maximum proton and deuteron energies of 20 and 10 MeV respectively) should produce neutrons of therapeutically acceptable intensity and having a penetration equal or better than that of the Hammersmith neutron beam.[16,21] However, work is still required on the optimum design of Li and Be targets, especially for smaller machines.

3. Improvement in the neutron mean energy.- There are various possible methods for increasing the mean energy of neutrons from a nuclear reaction without changing the bombarding conditions. These are :

(a) One method involves the use of a "thin" (or only moderately-thick) rather than a thick target, and a suitable backing material.

We demonstrated by our calculations for the ^{7}Li (p,n) reaction, that a thin target, which reduces the energy of 28 MeV protons to 23 MeV, would produce a neutron spectrum with a mean energy of around 19 MeV, instead of about 15 MeV from a thick target.[15] Of course, the neutron intensity from these targets would be correspondingly lower. Similar results have been experimentally observed for the Be (d,n) reaction and different thicknesses of Be. Parnell obtained neutron mean energies of 7.7 and 8.2 MeV respectively when he used thin Be-targets, 101 mg/cm^2 and 51 mg/cm^2 thick (which reduced the 16 MeV deuterons to 11 and 13.5 MeV respectively) instead of a thick one which would have given him a mean energy of only 7.0 MeV.[25] In the same way, Meulders et al[13] were able to increase the mean energies of the neutrons produced by 33 MeV deuterons from 15.3 MeV (for a thick target) to 17.0 and 17.5 MeV by using 1.1 mm thin Be-targets on copper and gold backing respectively. Their results also demonstrated the role of the backing material on the resultant neutron mean energy. This material should ideally produce as few neutrons as possible in order to have the least influence on the mean energy of neutrons produced by the target.

(b) The second method for improving the mean energy of neutrons, and hence their penetration, is to attempt to filter the low-energy neutrons without affecting the high energy ones to any great extent. The obvious choice for the filter material seems to be polyethelene, or any other hydrogenous substance, although copper filters have also been tried, but without any success.[22] By using polyethelene filters of different thicknesses, various authors have improved their neutron beams. These results are summarized in table 1.

Table 1. The effect of filtration on neutron mean energy or 50% depth dose

Beam	$(CH_2)n$	En (MeV)	Depth for 50% dose	Ref.
30 MeV p-Be	0	14	-	26
30 "	5.52 g/cm^2	14.8	-	26
40 "	0	17.6	-	26
40 "	5.52 g/cm^2	18.5	-	26
26 "	0	-	10.2 gm/cm^2	21
26 "	6.0 cm	-	11.9 "	21
35 "	0	-	11.4 "	21
35 "	6.0 cm	-	13.3 "	21
45 "	0	-	13.1 "	21
45 "	6.0 cm	-	15.3 "	21

Table 1 - (cont'd)

Beam	$(CH_2)n$	En (MeV)	Depth for 50% dose	Ref.
41 MeV p-Be	0	14.6	-	22
41 "	6.0 cm	19.5	-	22
90 "	0	42	15 cm	23
90 "	10 cm	44.6	17.5 cm	23
101 "	0	47.5	17.5 cm	23
101 "	10 cm	51.4	20 cm	23

Similar improvements have also been reported by Bewley et al for 45-75 MeV protons on Be and a 5.0 cm thick polyethelene filter.[24]

However, it must be mentioned that, as expected, there is a certain loss of neutron intensity due to filtration,[21-24,26] but this loss would not be drastic and would not affect the usefulness of various neutron beams, described in table 1, for therapy.

4. Current problems.- There are still a number of current problems in this field where nuclear physicists and engineers could contribute quite profitably and help the medical community. Some of these problems are :

a. Accurate neutron spectra measurements:-

There still exists a great discrepancy regarding the correct shape of thick target netron spectra from the Be(d,n) reaction. On the one hand, the data of Parnell,[25] for a deuteron energy of 16.7 MeV, shows a single, broad, high energy maximum in the neutron yield, with a monotonic decrease down to about 1 MeV. On the other hand, the data of Lone et al[16] shows, in addition, a very steep rise in the yield below 2 MeV. The data of Meulders et al,[13] which extends down to 2.5 MeV, also shows what could be interpreted as the beginning of a rise at lower energy. This low peak has also been observed by Weaver at 22 MeV deuteron energy.[27] So the important question arises whether this intense low-energy shoulder exists in the spectrum or not?

Similarly, most of the spectral data on (d,n) and (p,n) reactions extend only down to about 5-10 MeV, and very little information is available on the low-energy neutrons. From the shapes of various spectra, and from the depth-dose characteristics, it is expected that the flux of these low-energy neutrons is likely to be quite substantial, but this needs experimental verification. From a therapy point of view, these neutrons are very important, as they would be quickly absorbed in the first few mm of the body (skin, etc.) and impart large doses. Moreover, an accurate knowledge of the entire therapy neutron spectra is also needed for exact dosimetry calculations.

b. Target designs :- As mentioned earlier, Li-7 would, perhaps, be the ideal nucleus to produce a therapy neutron beam. However, a suitable Li-target for routine production of neutrons by cyclotrons is yet to be designed.

c. Filtration:- It has been discussed that the use of polyethelene filters removes some of the low-energy neutrons and hardens the beam. However, a great deal of work still needs to be done in this particular area in order to find out the optimum composition and thickness of the "filter" for different types of neutron beams. Either experimentally, or by Monte Carlo calculations, one could study the effect of different materials and/or their combinations and various thicknesses, on neutron spectra from different types of nuclear reactions and target systems.

Due to their training and expertise, active nuclear physicists and engineers are better equipped to solve such problems than ordinary hospital/medical physicists.

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