CYCLOTRON PRODUCTION OF FAST NEUTRONS FOR THERAPY

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SUMMARY

A brief review of the historical development of production of therapy neutron beams, with special reference to our own contribution using the available nuclear data, is presented. Different nuclear reactions and target systems have been critically examined regarding their suitability for cyclotrons of different sizes. A few current problems in this field, especially relating to the non-availability of appropriate nuclear data, where the nuclear physics and nuclear engineering communities can greatly contribute, are highlighted. Specific recommendations are made as to what sort of nuclear data needs to be acquired/compiled, that would be most useful in the neutron therapy programme.

1. INTRODUCTION

The interest in neutron therapy, and the number of centres applying this mode of treatment, have grown considerably since the late sixties, when the Hammersmith Hospital in London was the only institution seriously involved in such a programme. Besides, there are a number of academic and research institutions around the world which are engaged in physical and biological research connected with neutron therapy. However, in spite of all this, the true value and potential of neutron therapy has yet to be properly assessed, because of the inadequacies in the quality of the neutron beams used and the technical difficulties involved in the production of more suitable ones.

From the therapy point of view, a suitable neutron source should be able to provide adequate dose rate, at a source to skin distance of around 100 cm, and have penetration of at least equivalent to that of ^{60}Co gammas and preferably of x-rays from modern linear accelerators.

It is generally regarded that a treatment time per fraction of more than 5 minutes, or at the most 10 minutes, 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 around 20 rads/min at the patient's position. Moreover, in order to have penetration equivalent to that ^{60}Co gammas, the neutron beam must have a mean energy of around 15 MeV. Of course, higher neutron dose rates and mean energies would be advantageous and welcome.

Most of the institutions engaged in neutron therapy produce the neutron beam using cyclotrons, although Batavia (Fermi Lab.) uses a linear accelerator, and a few institutions use D-T generators. The neutron beam produced by D-T generators has a mean energy of around 15 MeV, which is acceptable, but its intensity is far from being 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) are major technical problems. A number of groups around the world have been working for years to solve them. With the cyclotron-produced neutrons, the problem is just the other way around. Most cyclotrons, including the smaller ones, can produce adequate fluxes of neutrons, acceptable for therapy, by using deuteron-induced reactions on a Be target. However, the penetration of cyclotron neutron is limited, unless larger and more expensive machines are used. As a consequence, some institutions, using small cyclotrons for neutron therapy, have discontinued this programme. In order to produce higher mean-energy neutron beams, larger machines have been installed at Seattle in the U.S.A. and Clatterbridge in the U.K., and the results from these institutions are anxiously awaited.

Since the late sixties, we have been examining alternative methods of improving the mean energy and hence the penetration of cyclotron neutrons, not by using bigger machines but alternative nuclear reactions and target systems. In this approach, we not only made full use of the existing nuclear and atomic data, but also constructed our own empirical data when no experimental of theoretical results were available, and achieved a great deal of success.

This alternative approach of improving the penetration of cyclotron neutrons, which should be a lot simpler and cheaper; its historical development and success, along with the role of nuclear scientists, are the main themes of 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. Most institutions, with the exception of a few Laboratories, have been using this reaction. 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]

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

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 phenomenon 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.

As early as 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. For this purpose, we made extensive use of the available forward direction (0-degree) absolute cross-sections, and angular distribution of the (d,n) and (d,np) reactions on deuterium. We calculated the 0-degree yield and thick-target neutron spectra, and the corresponding neutron dose at 100 cm from a deuterium target, for different incident deuteron energies of up to 16.7 MeV (the energy of the Hammersmith cyclotron). It was on the basis of these calculations that we were able to demonstrate in 1969, 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 neuterons 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 some institutions who are using, or planning to use, deuterium gas as a neutron producing target in their cyclotrons. The use of the deuterium gas target is, however, technically more complex than using a thick Be target. Special '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 into the target, instead of completely stopping it, one could still produce a therapeutically acceptable neutron beam.[10] Also, it is a lot easier to construct a cell for holding 3 or 5 atm. of deuterium 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 deuterium target. However, what surprised us most was the result that, in spite of the large difference in the Q-values of d + D and d + T reactions (3.8 and 17.6 MeV respectively) there was little different 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 deuterium) and 12.3, 12.6, 13.3 and 14.8 MeV (for tritium) 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 thresholds for this reaction from deuterium and tritium are 4.4 and 3.7 MeV respectively. Its cross-section icnreases rapidly with increasing deuteron energy. These neutrons have much lesser energy than the (d,n) neutrons and, due to their larger 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.

At that time there were no thick target neutron spectra conveniently available in the literature for proton-induced reactions on light nuclei such as Li, Be, etc. in the energy range of our interest. Therefore, 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 an 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 was extremely pleasing to note that these average energies, which had 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 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[18-26]. Most of the experimental arrangements used by these authors have a neutron-energy threshold 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. It is, therefore, quite likely that there are some low energy neutrons which could 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 liquid-Li target for cyclotron use.

Currently, a number of institutions around the world are using protons on Be as the neutron source for their therapy/radiobiology programme. These institutions are Fermilab, Seattle, Orleans, Houston, Louvain-la-Neuve and Clatterbridge.

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 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 17.9 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 metallic filters have also been tried, but with a lesser degree of success.[22,29] By using polyethelene filters of different thicknesses, and different additives, various authors have improved the mean energies and hence the penetration of their neutron beams.[22-26,28-31] However, it must be mentioned that, as expected, there is a certain loss of neutron intensity due to filtration,[21-26,28-31] but this loss would not be drastic and would not affect the usefulness of various neutron beams.

4. CURRENT PROBLEMS AND NUCLEAR DATA REQUIREMENT

There are still a number of current problems in the field of therapy neutron production, where the nuclear science community can substantially contribute and help their medical colleagues. Some of these problems are :

(a) Accurate measurements of (d,n) and (p,n) thick-target neutron spectra

There still exists a great discrepancy regarding the correct shape of thick target neutron spectra from the Be(d,n) reaction. On the one hand, the data of Parnell,[27] 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.[32] 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) (p,n) Nuclear reactions : general

As already mentioned, proton-induced reactions on lighter nuclei offer the possibility of producing the most suitable neutron beams for therapy. Therefore, accurate measurements and compilation are needed on the cross-sections, angular distribution and thick target spectra of proton-induced reactions on Be, ^{7}Li, C, Deuterium and H_2O, for proton energy of up to 100 MeV. As mentioned in Section (a), it would be necessary to extend the neutron spectrum measurements from thick targets down to a few hundred keV. Information is also needed on the production of cross-sections of the accompanying gammas from different nuclei.

(c) Target designs

Information is also required on practical design of thick and semi-thick targets of the above-mentioned nuclei, which would produce the most suitable therapy neutron beam, and of the corresponding backing material.

(d) Transport calculations/measurements

Calculations, and possibly measurements, of the transport of neutrons produced from different elements through tissue-equivalent media. This is of basic importance in neutron therapy. We believe that calculations, using appropriate transport codes and cross-sections, should be a lot easier and convenient than experimental measurements. In fact, for a neutron beam produced by 16 MeV deuterons on Be, we have demonstrated that different transport codes can provide results which are in good agreement with the existing experimental data.[33] Therefore, it could be possible to calculate the transport of higher energy neutron beams through the tissue-equivalent media using the same or improved codes. Of course, relevant neutron cross-sections on tissue constituents H, C, N, O, P, Ca, etc. would need to be compiled or measured.

(e) Filteration

It has already been discussed that the use of certain 'filters' removes some of the low energy neutrons and thus 'hardens' the neutron 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 'filters' for neutron beams produced through different nuclear reaction, target systems and bombarding energies. One could study the effect of different materials and/or their combinations, and various thicknesses, on the abovementioned neutron spectra, either experimentally or by transport calculations.

(f) Design of the collimator and the 'neutron head' shielding

The cross-sections and angular distribution of neutrons and the associated gammas from the (n,xn) reactions on C, Fe, Cu and W, for neutron energies of up to 100 MeV are urgently needed.

This information is necessary for the design of the collimator and 'neutron heads', especially for high energy neutron beams (Seattle, Clatterbridge, etc.) which are going to be used for therapy in the very near future.

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