# SURVEY OF THE "PRETHERAPEUTIC" EXPERIMENTS WITH FAST NEUTRONS PRODUCED WITH THE 50 MEV DEUTERON BEAM OF CYCLONE

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## Abstract

The physical and radiobiological experiments performed with the fast neutron beams at the cyclotron of the University of Louvain are described and discussed in view of their therapeutic applications.

## 1. Production of the neutrons

High energy isochronous cyclotrons, producing beams of high intensity allow to perform neutron-therapy in safe and reliable conditions with the required "physical selectivity".

The neutrons are produced by acceleration of deuterons on a thick $^{9}Be$ target ; three energies are currently used at CYCLONE : 16 MeV, 33 MeV and 50 MeV, comparable to the cyclotrons of Hammersmith, N.R.L. in Washington and Texas A & M respectively. The neutron spectra have been measured with the time of flight method [1] and the dosimetry with tissue equivalent (T.E.) ionization chambers and proportional counters (G.M., Rossi chamber) [2]. Increasing deuteron energy improves the physical characteristics of the neutron beam, like dose rate, depth dose and "skin sparing effect".

The table I summarizes the total dose (neutron + gamma) and the gamma contamination measured in air at a distance of 125 cm from the target with a 10 µA deuteron beam. The intensity of the neutron beams produced with deuterons at an energy higher than 30 MeV is sufficiently high to allow long source-skin distance (SSD) and the use of an efficient collimator system. Moreover the gamma contamination is low at these energies. The figure 1 shows the isodoses obtained at $E_d$ = 50 MeV in a 15 cm diameter irradiation field. The dose in depth is higher than for cobalt in a similar field ; on the other hand the "penumbra" is comparable. However, flattening filters are foreseen in order to compensate for the inhomogeneity due to the forward emission of the neutrons produced by the (d,n) reaction at this energy.

## 2. Dosimetry

The dosimetry is based on a "reference" T.E. ionization chamber. This chamber was provided by the group of N. Parmentier from the CEA under a research contract. A two step procedure is routinely used :

1) The chamber is calibrated in a reference Co beam before and after each run.

2) The absorbed dose in tissues is evaluated for neutrons by using a conversion factor $\overline{W}_\gamma/\overline{W}_n$ = 0.96 at $E_d$ = 50 MeV. This conversion factor is still an evaluation at this energy and can be revised later on. However, clear mention of this value should make comparison easier between different laboratories.

Integration of the deuteron beam current on the target is used as monitor, it can detect any drift during the experiments.

Moreover, direct comparisons with other laboratories are currently made in order to check the successive steps of the dosimetric system.

## 3. Collimator

The actual collimator consists in an alternation of steel, lucite and lead layers as shown in figure 2. Its composition has been determined by measuring the attenuation of the neutron beam in different shielding materials with the time of flight method coupled with pulse shape discrimination technique [4]. Several irradiation fields have been used : 20 x 20 cm (f.i. for total body irradiation in mice) and 19 x 4 or 19 x 3 cm (for selective irradiation of intestine or lung in mice). Field definition is measured with small size T.E. chamber (1.5 cc) and slow emulsion films placed behind a polyethylene converter. The film technique allows a rapid control of the position and the homogeneity of the neutron beam.

## 4. Radiobiological experiments

### 4.1. Relative biological efficiency (RBE) as a function of the neutron energy

In a first series of experiments, the RBE has been measured at $E_d$ = 16 MeV, 33 MeV and 50 MeV for single dose irradiation.

The following criteria have been used :

Chromosome aberrations is pig's lymphocytes and onion cells as a function of the absorbed dose.

Total body irradiation in mice : the 50 % lethal dose (LD 50) for the intestinal death (at 5 days) and the medullar death (at 30 days).

Both types of experiments show a steady decrease of the RBE by increasing the energy of the incident neutron beam ; f.i. the RBE for the intestinal death decreasesfrom 2.4 at $E_d$ = 33 MeV to 1.9 at 50 MeV.

### 4.2. Tolerance of normal tissues for fractionated irradiation

In view of its important therapeutic implications, our attention has been focused on the tolerance of healthy tissues irradiated by fast neutrons. The experiments were started with the neutron beams produced by the 50 MeV deuterons ; this energy will probably be used in the first radiotherapeutic applications.

Proc. 7th Int. Conf. on Cyclotrons and their Applications (Birkhäuser, Basel, 1975), p. 431-435

a) Early recovery of intestinal stem cells in mice was assessed using the classical split dose technique. LD 50 was measured for single fraction and two equal fractions separated by a time interval of 1 h 30, 3 h 30 and 5 h 30 (figure 3). Increase of LD 50 was much lower for neutrons (< 30 rad) than for gamma irradiation (≈ 250 rad).

b) This study had to be completed by the determination of the RBE of the neutrons for lower doses per fraction : as a matter of fact usual treatments are given with daily doses of 200 - 300 rad. For this aim, increase of LD 50 has been evaluated when N fractions are divided in 2N equal fractions. Preliminary analysis show that for N = 3, LD 50 raises from 825 rad to 885 rad. When N = 5, no further increase of LD 50 is observed (LD 50 = 875 rad or 5 x 175 rad) (figure 4). This suggests that the tolerance dose for intestine evaluated from the LD 50 does not increase with the number of fractions if the dose per fraction is lower than 175 rad. By using the 19 x 4 cm collimator, it is possible to irradiate selectively the abdomen of 4 mice simultaneously and to avoid the medullar syndrome.

### 4.3. Study of the RBE for low doses

The induction of chromosome aberrations in onion roots (Allium cepa) has been measured with the neutron beam produced at $E_d$ = 50 MeV. This system is sensitive to low neutron doses : 10 - 40 rad.

This study presents two points of interest :

- from a radioprotective point of view, it is important to know the RBE for low doses. It is known that for certain biological effects the RBE may dramatically increase when the dose diminishes ;
- from a theoretical point of view, it helps to determine the dose-effect relationship and the RBE-dose relationship for chromosome aberrations. The linear and quadratic component ($\alpha$,$\beta$) of the dual radiation action proposed by Kellerer and Rossi [5] could be evaluated from these data.

Two criteria have been used :

- percentage of cells in anaphase and telophase showing at least 1 aberration ;
- mean number of aberration per cell in anaphase and telophase. The results indicate for the two criteria a variation of the RBE from 6.5 to 11 by decreasing the dose from 40 to 10 rad. This shows that one ought to be careful before extrapolating the RBE values measured for high doses (RBE ∿ 2) to the low dose region (figure 5).

### 4.4. Other experiments in progress

In collaboration with the group of G.W. Barendsen (Rijswijk - The Netherlands), cell survival curves were measured "in vitro" for human T-1 kidney cells.

A study of long term effects on the lungs similar to that performed on intestine is underway. Lungs in mice are irradiated selectively with a field 3 cm in height.

Finally, study of the radiotherapeutic effect of fast neutrons on grafted tumours is planned at the end of this year.

## 5. Conclusions

The dosimetric and biologic experiments performed during the last two years at Cyclone give the necessary information in order to start patient irradiation under safe conditions. The treatment building is under construction (figure 6). The deuteron beam will be transported outside of the actual experimental hall and deflected downwards to the irradiation room. The neutron beam from the $^9$Be(d,n) reaction being mainly peaked in the forward direction [1], a pit is foreseen in order to trap the neutrons and to reduce the background in the treatment room. Finally, a variable collimator is under study.

With thank Y. Jongen, G. Ryckewaert and the Cyclotron Staff for efficiently running the machine and the "Fonds de la Recherche Scientifique Médicale" together with the "Institut Interuniversitaire des Sciences Nucléaires" (Brussels) for financial support.

### References

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2. N. Parmentier and Al., Proc. of Conf. on "Biological Effects of Neutron Irradiation" IAEA (1974) 59.
3. A. Bridier and P. Fache, Thèse de Doctorat (1974) CEA-R-4655.
4. J.P. Meulders and Al., Proc. of 2nd Symp. on "Neutron Dosimetry in Biology and Medicine" IAEA (1974) 811 and N.I.M. 126 (1975) 81.
5. A.M. Kellerer and H.H. Rossi, Rad. Res. 47 (1971) 15.

Table I.- Neutron and gamma doses measured in air at a SSD = 125 cm ($I_d$ = 10 μA) [3]

| Deuteron energy (MeV) | Dose rate (n + γ) (rad/min) | γ Dose/total dose % |
|---|---|---|
| 16 | 4.88 | 6.7 |
| 33 | 41.50 | 2.9 |
| 50 | 154 | 2.8 |

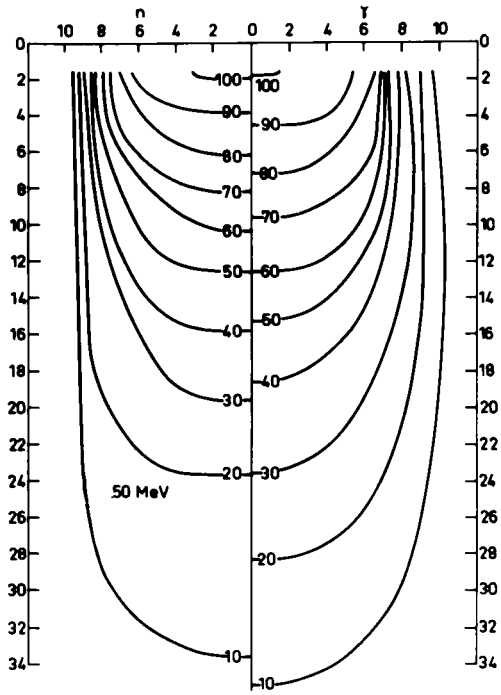


Fig. 1.- Dose distribution in a tissue-equivalent medium measured in a plane containing the beam axis for neutrons produced by 50 MeV deuterons (SSD = 125 cm, 15 cm in diameter)

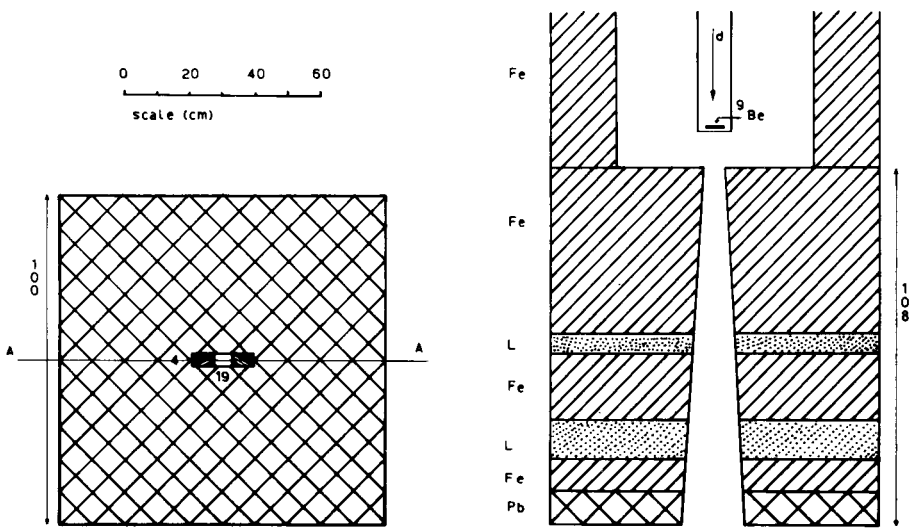


Fig. 2.- Front view and horizontal section (containing the beam axis) of the 19 x 4 cm neutron collimator (Fe = steel, L = lucite, Pb = lead)

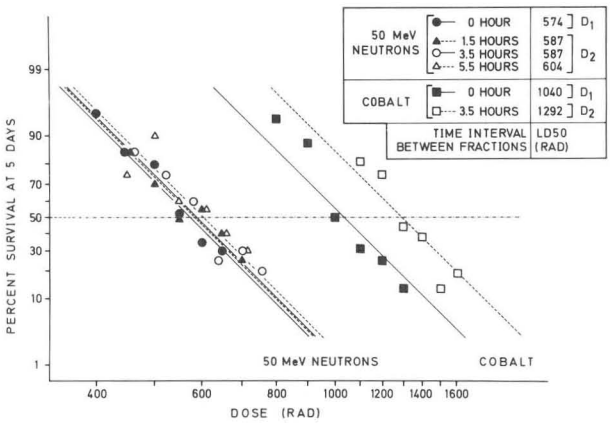


Fig. 3.- Irradiation of abdomen in mice. Survival/dose relatioships for an irradiation consisting in a single dose and 2 fractions separated by 1 h 30, 3 h 30 and 5 h 30

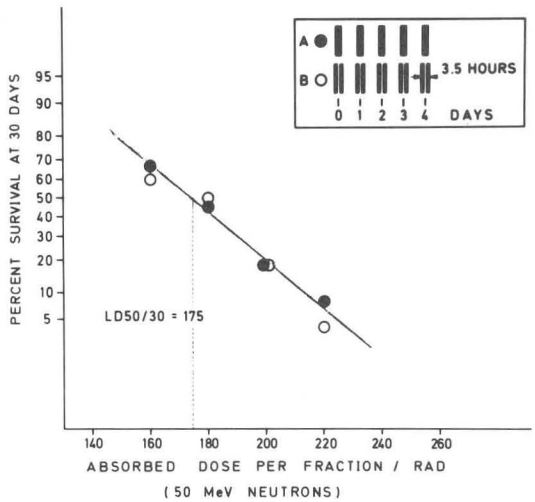


Fig. 4.- Irradiation of abdomen in mice. Survival/dose relationships for an irradiation consisting in 5 equal fractions 24 h apart and for each of the 5 fractions splitted into 2 equal sub-fractions separated by 3 h 30

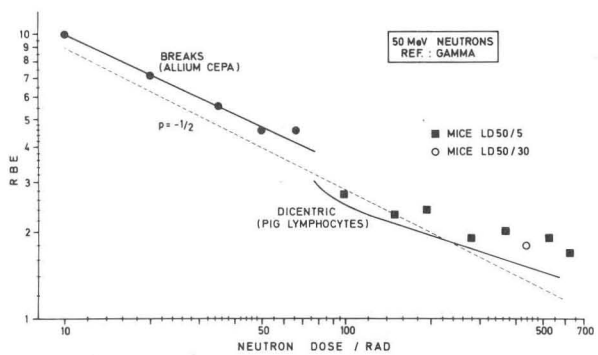


Fig. 5.- Survey of the RBE-dose relationships for the different biological experiments at $E_d$ = 50 MeV

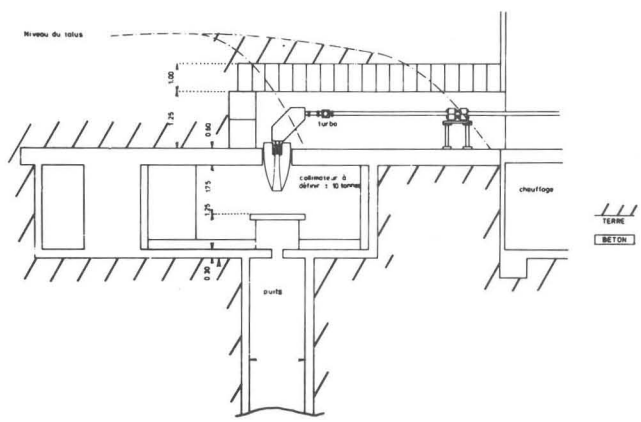


Fig. 6.- Idealized view of the planned therapy facility

## DISCUSSION

T. KUO: You mentioned the neutrons were produced by 50 MeV deuterons on Be, but 50 MeV neutron energy was indicated on your slide. Would you comment on this discrepancy? What is the average energy of the neutrons?

J.P. MEULDERS: The indications on the slide always referred to the neutrons produced by a 50 MeV deuteron beam; the mean energy of the produced neutrons is close to 20 MeV.

M.A. CHAUDHRI: Did you try to use other targets than Be for neutron production? Our results have shown that much cleaner neutron spectrum would be produced by interacting high energy protons on a $^{7}$Li target.

J.P. Meulders: Yes, we measured the neutron spectra from the (d,n) reaction on a series of elements from $^{9}$Be up to $^{197}$An. You are right that cleaner spectra are obtained by accelerating protons on a thin Li target but the dose rates of the neutrons produced by this reaction should be insufficient for therapeutic applications; e.g. a 50 MeV deuteron beam of 10 μA incident and a 3 mm thick $^{7}$Li target ($\Delta E_p \sim$ 2 MeV) should produce a dose rate of 2 rad/min at 1 m from the target.

M.A. CHAUDHRI: No matter what your target is, you would always get plenty of break-up neutrons with much lesser energies when you are using deuterons of more than a few MeV for bombardment. The higher dose rate produced from Be may not be of great significance as you are getting enough dose-rate with almost all your targets.

J.P. MEULDERS: The neutron spectrum from the $^{9}$Be(d,n) consists of a broad peak centred at $E_n$ = 21 MeV. It is clear that the main contribution comes from the break-up of the deuteron. However, the mean energy of the produced neutrons is higher in the case of the Be target than for the other targets. Moreover, the gamma contribution is the lowest in this case.

M.A. CHAUDHRI: Did you consider using a deuterium gas target for neutron production? Our experience is that much better neutron beams are produced by the interaction of deuterons than on Be under similar bombarding conditions.

J.P. MEULDERS: We did not consider a deuterium gas target for neutron production for the radiobiological and therapeutic applications, although we have such a target for polarized neutron beam purposes. Producing high neutron fluxes from such a target implies a cryogenic installation which is not practical to use in routine biological experiments like fractionated irradiation. A Be target on the contrary is easy to handle and of unlimited use.