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NEUTRON THERAPY—THE HISTORICAL BACKGROUND

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Neutron therapy was first introduced by Stone et al. in 1938, i.e. more than 10 years earlier than electron beam therapy and only 6 years after the discovery of neutrons. In spite of the impressive accomplishment in generating an adequate therapy beam, time was also found for careful radiobiological studies of neutron beams. However, it was not considered that for a certain early reaction the late effects were much greater with neutrons than with x-rays. The severe late sequelae in proportion to the few good results motivated the closure of this therapy. Neutron therapy was again introduced in Hammersmith hospital at the end of the 1960's. The major reason seems to have been to overcome the oxygen effect. Encouraging results were reported. It was argued that the very favourable statistics on local tumour control were obtained at the expense of more frequent and more severe complications. A clinical trial in Edinburgh seemed to indicate this, but it was not proved in the end as the two trials differed regarding fractionation. Today about 16 000 patients have been treated with neutrons. The neutron beams now used differ significantly, both regarding dose distributions and microdosimetrical properties, from those utilized earlier. The advantage of neutrons is still, however, controversial. There are indications that neutron treatment may be favourable for some tumours. A careful cost–benefit study ought to be performed before the creation of a neutron therapy centre in Sweden as the group of patients suitable for neutrons is limited, and there may be new possibilities for improvement of photon and electron treatment with much smaller resources.

Heavy equipment for radiotherapy is fairly expensive. It is therefore of importance that the resources are well utilized. In 1991, the National Board of Health and Welfare in Sweden published general recommendations for the health authorities concerning coordination of oncologic care, based on a report from an expert committee. The authors of the present paper were responsible for an appendix to this report on heavy radiotherapy equipment, including recommendations based on a broad consensus among all the radiotherapy departments in the country (1). At that time there were some recent positive reports on the results of using neutron therapy, and it was suggested that 10 to 20% of all cases would be better treated with neutrons than with x-rays or electrons (2). It was also assumed that neutron therapy was indicated in less than 5% of the radiotherapy patients and that this, in 1995, could be taken care of by 2 neutron therapy units.

There are, however, different opinions on the usefulness of neutrons in radiotherapy (3–5). Furthermore, it must also be judged from the cost–benefit point of view as to whether this is the best investment for cancer patients. The present paper will give the historical background of neutron therapy which is of importance for the present decisions regarding possible new neutron projects.

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Treatments by Stone et al.

The principle of the cyclotron was conceived early in the 1930's by E. O. Lawrence at the University of California and a first apparatus was built in 1931–1932 (6). Lawrence and his associates continuously developed the cyclotron

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during the following 10 years. A cyclotron with an 80-ton magnet producing 8 MeV deuterons was ready in 1936 and one with a 190-ton magnet giving 16 MeV deuterons was in operation in 1939. These two units were used for the therapy.

Chadwick discovered neutrons in 1932 (7). The method of using the cyclotron to produce neutrons, and some of the properties of neutrons were described by E. O. Lawrence (8) to the Radiological Society of North America in 1936. This intrigued Stone and his group, who decided to investigate the possibility of using neutrons in radiotherapy. Before any treatment of cancer patients was initiated, a considerable amount of biological experiments was carried out (9–13, and personal communication with Aebersold & Anslow). It was clear to Stone that the biological effect of neutrons, compared to x-rays, varied considerably for different biological systems. In 1938 it was felt that animal experiments could not answer the question as to whether neutrons would be better than x-rays for human cancer treatment. From September 1938 to June 1939, 24 patients were treated with the neutron beam generated from 8 MeV deuterons on beryllium. All patients had advanced cancer. Generally, they received only a single irradiation, with skin doses that seem to have been between 1.5–6.5 Gy (14).

In parallel since 1937 the development of a larger cyclotron took place. This cyclotron was operational in June 1939 and neutron treatments started at the end of 1939 and continued up to 1943; 226 patients were treated during that time. The depth dose distributions from this beam were very similar to those for the 250 kV x-ray beams commonly used at that time. A collimating device which gave fields of varying sizes for a fixed horizontal direction was developed (15).

The patients selected for treatment in this second series were also, with a single exception, considered incurable by any other means. The treatment of the one curable patient, here summarized as an illustrative example, was described by Stone in 1948.

According to the biopsy, the patient had a laryngeal lesion, a squamous cell carcinoma. He was treated through two opposing lateral fields, each 7 cm × 7 cm. Nineteen treatments were given in 48 days, with a total dose of 500 n to each skin surface. The n was a special unit and its value was derived by measuring with a Victoreen 100 R chamber and using the calibration factor exposure, i.e. röntgen per meter reading, at conventional x-rays. One n corresponded to about 2.5 cGy or rad according to Stone (15) and 500 n would thus correspond to about 12.5 Gy. Cross-section dose plans were not carried out. If the exit dose from the opposed field is considered, about 20 Gy would have been given, in 19 treatments over 48 days. Stone reported that no treatment was considered complete unless a good erythema was produced and in the majority of cases some degree of epidermolysis was produced. Fig. 1 shows the reaction after 38 days, following the start of treatment. The reaction 5 years later is seen in Fig. 2. At that time the patient had fixations of the skin and the subcutaneous tissue to the larynx—the whole area felt very hard. Stone was of course not content with the treatment, as the patient might have been cured with much less damage to normal tissue using conventional x-rays.

Stone analysed his material very carefully (15). It was especially stressed that, in comparison with x-rays, the late

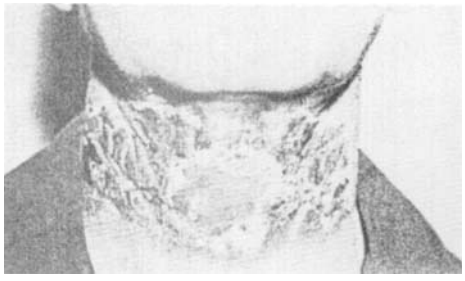

Fig. 1. Acute reaction, 38 days after starting treatment. The treatment continued up to 48 days with three fractions a week. The irradiations were given through two opposing lateral fields. The total dose to the target volume seems to have been about 20 Gy. (From AJR 1948; 59: 771–88 by R. S. Stone).

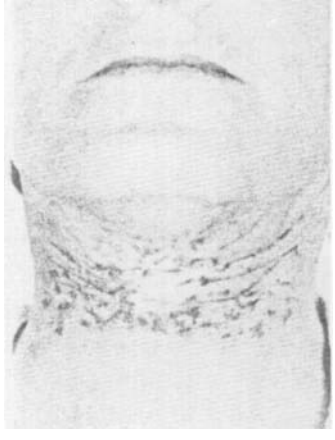

Fig. 2. The same patient as in Fig. 1. The chronic reactions are seen. (From AJR 1948; 59: 771–88 by R. S. Stone).

reactions were much more pronounced than would have been expected from the early reactions. It was concluded that 'neutron therapy as administered by us (i.e., Stone et al.) has resulted in such bad late sequelae in proportion to the few good results that it should not be continued'.

Hammersmith experience

In the 1950's, the interest in fast neutrons was renewed, mainly due to extensive studies by Gray et al. (16) on the influence of oxygen on the radiation sensitivity of different biological materials. Neutron radiation was considered to be advantageous when tumours containing hypoxic cells were irradiated. It was further argued that the poor results obtained by Stone were due to poor understanding of the radiation biology. Fowler et al. (17, 18) pointed out that because of less recovery between fast-neutron fractions, the doses are more additive than for x-rays and that the total dose might have been too high. Neutron therapy was therefore again introduced at the Hammersmith hospital in the end of the 1960's. The cyclotron had a beam fairly similar to that used by Stone, i.e., 16 MeV deuterons on beryllium.

Again, patients with advanced tumours were chosen. Catterall reported encouraging results for patients treated

up to January 1973 (19). In all, 238 patients had then completed their treatments. Catterall was aware of the importance of a good dose distribution. She states 'The techniques of fast neutron therapy are much more demanding than those of low LET radiation; the margin is narrow between the dose leading to recurrence and that resulting in necrosis'. Modern dose planning was performed, e.g. wedge filters of polystyrene were used to improve the dose distribution and all patients treated for head and neck tumours were fixated in bexoid shells. There were, however, technical constraints as the beam was fixed and horizontal, and the penetration corresponded to 250 kV x-rays. The standard treatment by Catterall was 14.4 Gy delivered in 12 treatments over 26 days. The first report from Catterall resulted in a new interest in neutron therapy. In two randomized trials, results from neutron and photon treatment for advanced head and neck tumours were compared. It was concluded that there was a strong advantage for neutrons, with 76% local control rate, compared to 19% for photons (4). However, follow-up was short in most of these patients and the differences in treatment-related complications were not fully judged. A subsequent paper reported significantly more severe complications in the neutron treated patients (20).

A cyclotron of very similar neutron energy was installed in Edinburgh in the mid 1970's. One aim was certainly to have an independent verification of the positive results reported by Catterall et al. A new trial on head and neck cancer was performed from 1977 to 1982 (3). This study failed to demonstrate any advantage for neutrons but reported increased toxicity. Unfortunately, there were differences in the fractionation schedules which did not make the two trials completely comparable. The Medical Research Council (MRC) formed a working group to reveal the reasons for those differences. It was stated that 'a full appraisal of its (neutron therapy) place, both for certain stages of specifically selected tumours and in the context of general clinical oncology, will have to await the outcome of a new generation of trials now being planned which will utilise machines producing higher-energy neutrons with dose distribution comparable to those of megavoltage photons' (21).

The present situation

Physics. Twenty-eight neutron therapy facilities have been used for radiotherapy. In a list by Maughan (22) it appears that there were 21 operational units in 1992; 17 of these were cyclotrons, 3 were D-T generators and one was a linear accelerator. It seems that D/T generators are no longer considered to be of interest. Recent units are generally supplied with rotational gantry and variable collimator or even leaf collimator (22). Most units use the (p, n)Be to produce neutrons with proton energies between 30–60 MeV. The cost of these units is fairly high, in particular due to the complicated beam transport system. The isodose distributions are comparable with those of x-rays from 4–6 MeV linear accelerators.

In fast-neutron interaction with tissue, most of the energy transfer is through proton recoils. The energy deposit per unit path-length is much higher than for electrons in the energy range of interest in therapy. The deposition rate varies, however, with the neutron energy. For instance, a modern cyclotron facility with 65 MeV protons on beryllium produces neutrons with a mean energy of about 28 MeV and protons of about half that energy is generated in tissue. The linear stopping-power for such protons is about 40 MeV cm^{-1}. The facilities by Stone, Catterall and Duncan generated beams with mean neutron energies between 6 and 7 MeV and therefore recoil protons of about 3 MeV; the linear stopping-power being about 150 MeV $\cdot$ cm^{-1}. The corresponding linear stopping-power for electrons, for electron and photon beams used in therapy, is about 2 MeV $\cdot$ cm^{-1}. This is of course a very simplified calculation as it is not considered that the linear stopping power increases as the protons are slowed down and that there are also neutron interactions with heavy nucleus in the tissue. The example illustrates, however, that the biological effect from old and modern units is not fully comparable. The RBE for different biological systems varies in this energy range by a factor of 1.5–2 (23). The difference in RBE between various modern high energy neutron units is, however, moderate, not more than 15–20% (24).

A most useful way to characterize the different beam qualities is through microdosimetrical measurements. Such measurements directly show the number of energy depositions in a small volume of about the same size as the radiation sensitivity volume of a cell. Very often, a diameter of 1 μm is considered in such measurements. There are large statistical fluctuations in the number of energy deposition events between different cells for neutron radiation. For instance, one 'cell' out of two (diameter 1 μm) will be missed if 1 Gy of 14 MeV neutrons is used for the irradiation. With photons or electrons instead, as a mean, about 20 energy transfers will take place in a volume with $\varnothing$ 1 μm for 1 Gy, and of course the variation of energy deposits will be smaller between cells. It has been argued that the inhomogeneous microdosimetry dose distribution might be a greater problem for neutrons than the macroscopic dose variation (25). Mixed beams of neutrons and photons could be a way out of this problem.

Radiation biology. The rationale for neutron therapy during the 1970's was mainly the belief that many tumours contained a significant number of hypoxic cells which were better treated with neutrons than photons. Still, hypoxia seems to be an important argument for neutrons, but it is accepted that the reoxygenation during fraction reduces the population of hypoxic cells (26). There are to-day other ways to manipulate hypoxic cells, as described by Denekamp in this symposium (27).

The radiosensitivity of a cell for neutron radiation is less dependent on the phase of the cell cycle than with photons. This could be an advantage for neutrons for some slow-growing tumours with cells spending long periods of time in the radio-resistant G1 phase.

Finally, compared to photons, the repair of sublethal and potentially lethal damages is reduced. This is generally a disadvantage for neutrons as it effects the recovery of normal tissue. However, some tumours as melanomas have generally a very high repair capacity which is why neutrons might be advantageous.

Clinical indications. What are the clinical indications for neutron beam therapy? Up to now, there is no consensus on this. In general, salivary gland tumours (5) and connective tissue sarcomas (5, 28) have been stated to be potentially suitable for neutron beam therapy. There are in all in Sweden each year (1989) about 80 new cases of malignant salivary gland tumours and 290 new cases of connective tissue sarcomas. Most of these patients will be treated adequately by surgery, and neutron beam therapy will then be limited to some patients in whom surgery is not feasible and where there are local problems from tumour, present or anticipated. One estimate is that such patients will account for less than 20% of all, and then the total number of such patients for whom neutron beam therapy could be considered is of the order of 75 per year in Sweden (population 8.5 million (1989)). Furthermore, neutron beam therapy has been reported to be useful in some cases of cancer of the prostate. The total number of new cases in Sweden each year is presently around 4800. The majority of these are not candidates for radical therapy, but the fraction presented with localized disease can be expected to increase with improvements in the diagnostic methods (biochemical markers, ultrasonography). One estimate is that less than 5% (around 200) patients could then each year be considered for neutron beam therapy for early carcinoma of the prostate. It should be recognized that this estimation is not based on extensive experience, and has to be regarded only as a guess. Other potential indications that have been discussed are bulky metastatic lymph nodes in the neck, unresectable rectal carcinoma, and high-grade astrocytomas.

Conclusion and Discussion

Modern neutron facilities differ significantly both regarding physical dose distributions and microdosimetry characteristics from most units installed before the 1980's. Earlier results are therefore not fully relevant for judgement of the usefulness of neutrons.

For most tumours there seem to be a stronger radiobiological rationale for using photons and electrons than neutrons as the concomitantly irradiated normal tissue is less affected. It seems also to be a general consensus that only a few types of tumours might be better treated with neutrons than with electrons and photons (28).

About 30 neutron facilities have been in use for radiotherapy, representing a considerable investment. About 16 000 patients have already been treated. It might seem astonishing that conclusive evidence for the usefulness of neutron therapy has not yet been presented. One reason for the failure might be that the neutron facilities have been suboptimal. Also, it might be a problem to set up trials large enough for revealing differences of 10 to 20% as some of the tumours suitable for neutrons are relatively rare. There is, however, one ongoing RTOG randomised trial (Radiation Therapy Cooperative Group) on prostate cancer which was started in 1986 and now has about 200 patients (5).

It might be accepted that there could be a niche for neutron therapy. However, there is today a broad development in photon and electron therapy, and so this niche might be taken over by more conventional and less expensive treatment techniques (27). Only further research can give the future direction.

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