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PRACTICAL REQUIREMENTS FOR THE TREATMENT OF PATIENTS WITH CANCER

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SUMMARY

There is great world-wide interest in the possibilities of fast neutron therapy of cancer. In order to meet the increasing demands for fast neutrons to treat patients, cyclotrons, constructed for other purposes, are being adapted for clinical work. Many however, are essentially unsuitable for this purpose. Other cyclotrons which are being constructed are technically inferior to the modern megavoltage X-ray or γ-ray apparatus routinely available in Radiotherapy Departments. There is, therefore, a great risk that misleading information will result from clinical studies using such equipment since this could reflect more the inadequacy of the delivery of neutrons to the tumour than the effects of neutrons themselves. Six factors are proposed which must be included in the production of a neutron machine in order that patients may be treated in a manner comparable to that using photons from the megavoltage machines now in regular use throughout the world.

One of the most interesting developments in radiotherapy at the present time is the establishment of fast neutron facilities and the clinical evaluation of the use of neutrons in the treatment of patients with cancer.

The introduction of modern megavoltage X-ray and γ-ray beams with their high degree of precision and efficiency have made it possible to deliver an exact dose of radiation to any defined tumour volume. This has resulted in a high probability of cure of many common cancers, with little associated morbidity. However, it is still true that a significant number of tumours are not well controlled by X-ray therapy. It was in the hope that the use of fast neutrons might overcome this problem of radioresistance that clinical studies of this form of radiation were first undertaken.

The early work was carried out by Stone and Larkin between 1938 and 1942[6], only a few years after the discovery of the neutron by Chadwick in 1932. There was no basic biological information available at that time to provide a rationale for the use of neutrons in preferance to X-rays. Further, even in those days, the treatment facilities afforded by the cyclotron were greatly inferior to those available for X-ray therapy. Although a few very advanced tumours were cured, there was an unexpectedly high incidence of late radiation morbidity which led, in part, to the abandonment of neutron therapy. A subsequent review of Stone's work by Sheline and his colleagues[5] demonstrated that the excessive damage produced in these early studies was due to excessive radiation dose. This was a result of a lack of understanding of the way in which neutrons produce their effects in tissues. The differing effects of fractionation of neutron treatment, compared with X and γ rays was not known at the time, so that proper allowance could not be made for treatment schedules which were erratic and rarely given as planned. In addition, poor technical treatment facilities made accurate treatment planning very difficult. These are factors of great importance to be considered as a priority when establishing new clinical neutron facilities.

Renewed interest in the possibilities of improving cancer therapy by neutron irradiation occurred in the late 1950's following a great deal of radiobiological work which had demonstrated possible explanations for the radioresistance of some tumours. The importance of the presence of oxygen in order for X-ray therapy to be fully effective became known. Since most solid tumours contain a proportion of malignant cells which are oxygen deficient, this may account for one of the principal reasons for radioresistance. It was also realised that all mammalian cells have a great capacity to repair much of the damage inflicted by X-rays during courses of treatment.

The lethal effects of neutron irradiation are much less influenced by the presence of oxygen and thus, theoretically, such treatment would be more effective in dealing with hypoxic, radioresistant tumour cells. Further, it has also been demonstrated, for a wide variety of tissues, that the ability of cells to repair sublethal radiation damage is markedly reduced after neutron irradiation compared to X-ray exposures.

In order that these biological advantages of neutrons may be fully utilised it is important that treatment machines be

A fixed horizontal beam treatment facility illustrating the difficulties which arise with this set-up in carrying out accurate treatments.

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developed which are the equal of modern megavoltage X-ray apparatus as far as is possible. At present all existing neutron sources suffer from serious disadvantages. For instance, the MRC cyclotron in Hammersmith Hospital has a neutron beam which is fixed in the horizontal position and is collimated in squares or rectangles of fixed sizes.

The low energy (7.5 MeV) gives a dose distribution only slightly better than 250kV X-rays and the isodoses are rounded and show a clinically significant penumbra. The Edinburgh cyclotron, which has the advantage of having an iso-centric treatment facility, still suffers from the beam being of an energy virtually identical with that at Hammersmith Hospital. As a result, skin reactions are produced which often proceed to moist desquamation before healing, and the treatment of abdominal and pelvic tumours can only be carried out in thin patients. Even in these, the dose distribution is frequently uneven and compares badly with that from ^{60}Co. Tumours of the head and neck can be given more uniform doses but even so, because of the penumbra of the beam, and rounded isodose curves, it is difficult to avoid vital structures such as the eye and spinal cord. Damage to these may therefore represent technical inadequacies of the beam rather than a specific effect of neutrons.

Megavoltage radiotherapy apparatus is always situated within special departments in hospitals where physicists and clinicians have wide experience in their use. Any additional medical or surgical care which is required for patients undergoing X-ray therapy is therefore readily and speedily available. In contrast, many neutron therapy facilities are situated at some distance from a hospital, as for example, at the M.D. Anderson Hospital in Houston, Texas and also in East Berlin. This poses the additional problem of transporting often ill patients many miles to have their treatments.

In spite of these disadvantages, in the one controlled clinical trial where statistically significant results are available, the neutron treated patients showed a highly significant benefit over those treated with photons[3].

Importantly, further work carried out in the same centre suggests that in addition, there may be real advantage for the use of neutron therapy in the treatment of those tumours traditionally regarded as being radio-resistant, for example stomach cancer and soft tissue sarcoma[1,2].

There are now increasing demands all over the world for fast neutrons to treat patients. This demand is being met by the conversion of cyclotrons constructed for other purposes, essentially unsuitable for clinical work, or by the production of neutron machines which technically fall far short of modern megavoltage X-ray machines.

Six factors which must be included in the production of a neutron machine suitable for treating patients were listed by Catterall (1976)[4]. They are as follows:-

1. <u>The beam must always be available to meet clinical requirements</u>.

Unless the total dose can be given in the number of fractions and overall time which were selected at the outset, this renders accurate comparison of clinical effects impossible. Should any morbidity develop subsequently, erratic treatments make it difficult to assess whether the chosen dose is too high or whether the effects produced are due to the pattern of treatment given.

If the machine is only available for certain periods during the year, randomized clinical investigations cannot properly be conducted and, in addition, unsatisfactory modifications to the treatment schedule may have to be made. For example, if the neutron facility is available for only six months of the year, clinicians are naturally anxious to utilise it to the full during this period. There is, therefore, a temptation to treat all patients suitable for randomization within a clinical study with neutrons during this period of time, and all other similar patients with X-rays during the following six months period. Such a method of randomizing patients is always open to criticism, for it is doubtful if the patients included in such a study could ever be considered to be truly similar. As a result, the clinical findings from such a centre may always be regarded with a degree of scepticism. Similarly, if the neutron beam is available only on certain days of the week or month, patients will be able to receive only a proportion of their treatment from neutrons, the remainder being given by X-ray therapy. Whilst there may be some merit in this form of treatment, it does make the assessment of the place of neutron therapy impossible and only delays further full understanding of the contribution which fast neutrons may make to the management of cancer patients.

In addition, from the patients' point of view, unreliability or non-availability is traumatic and produces intense disappointment and anxiety when treatment cannot be given. Also the tumour may continue to grow during the period of delay.

The reputation of a unit beset by such problems suffers and clinical colleagues grow sceptical about referring patients for treatment.

Clinical requirements must always have first priority. Competing claims for machine time or high cost of renting time can be reasons for administrators to withhold funds, causing interruptions to a clinical programme.

2. <u>The output must give treatment times not exceeding four minutes</u>.

Many patients with cancer are ill and are unable to withstand being immobilised for long periods of time, particularly if they are in pain. Prolonged treatment times, therefore, select patients who can maintain a certain position for the time demanded and make some positions impossible. Megavoltage machines can easily carry out treatments within two or three minutes and therefore, unless the neutron machine has a similar output, this may influence the clinical results obtained.

3. <u>Depth dose and isodose curves must be at least as good as those of ^{60}Co</u>.

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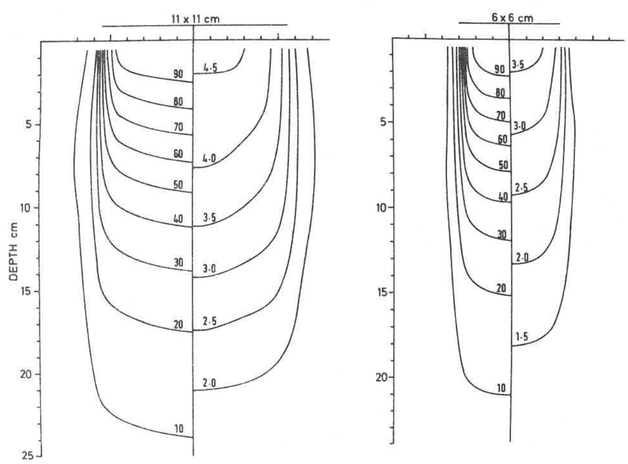
Megavoltage beams of X-rays with their increased penetration and sharply delineated edges have provided one of the most useful advances in the treatment of cancer. They have enabled tumours in any situation within the body to be treated adequately, whilst at the same time making it easier to protect adjacent normal structures.

Neutron beams must be comparable at least with those of ^{60}Co. Less penetrating radiation makes the treatment of deeply situated tumours impossible, and even in more superficial lesions, often the distribution of dose is uneven.

In these circumstances tumour recurrence becomes more likely as there is a danger that some parts of the tumour will receive an inadequate dose. Further, there is an increased risk of delivering high doses to vulnerable normal structures such as the spinal cord.



Isodose curves of 7 MeV neutrons showing on the right the γ component. Note the 50% isodose level is at only 8-9 cm.

4. <u>The neutron machine must be within a hospital</u>.

Radiotherapy departments for photon therapy are part of a hospital and any necessary specialized medical or surgical treatments are readily available. In addition, the treatment room, clinic and simulator are all adjacent to one another. There is no restriction placed upon the time necessary for the careful examination and accurate planning of patients. All members of the therapy team are highly trained and experienced in the clinical applications of irradiation.

Many neutron facilities, on the other hand, are situated at some distance from a hospital, utilising machines constructed for other purposes but adapted for clinical use. This, therefore, selects patients who can undertake the journey. The time, expense and distance may influence the total number of treatments given or the fractionation and may result in an inferior overall treatment. Inferior treatment planning or inadequate care in clinical examination may result from pressure on the clinician, knowing that only a limited amount of time is available on the treatment machine, some of which has been taken up by the time of the journey.

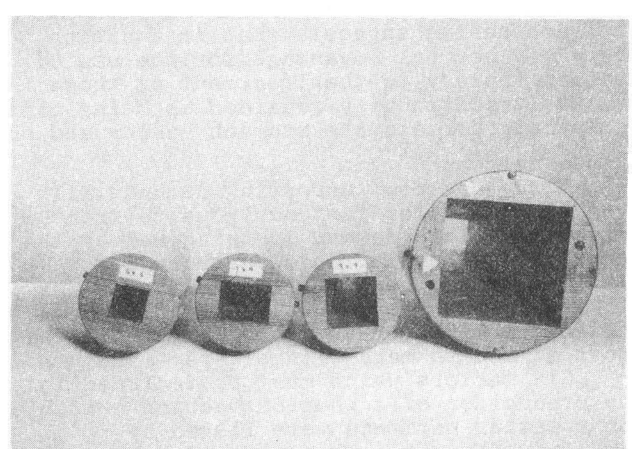
If long distances or unusual surroundings are involved, as might be the case in certain adapted facilities, they will usually have a deleterious effect on the patients involved and will certainly be different from the photon treated patients. In addition, certain members of the staff involved in such facilities may not be fully aware of the special considerations required when planning and treating patients, which may act to the disadvantage of those treated at that centre. So important are these factors that they would have to be considered when analysing the results of controlled clinical trials.

5. <u>The set-up of neutron treatments must not be compromised</u>.

The radiation hazard in the treatment room is of prime importance in this respect and is of particular importance as iso-centric facilities are being developed where the target itself is within the treatment room. Unless the radiation levels are sufficiently low to allow unhurried, careful treatment set-ups with precise patient positioning, there is the risk that beam alignment will be incorrect and as a result, parts of the tumour may be inadequately covered. There may be the added difficulty of persuading well trained staff to work under such conditions, thus further prejudicing the treatments. The problem of induced radiation must therefore dictate which materials are used in the construction of the iso-centric machine. Aluminium should be avoided wherever possible. Similarly, it is important that the mechanical tolerances of the iso-centric gantry are capable of coping with the weight of the required shielding material.

Collimators which are so heavy that they cannot be easily handled or quickly changed may lead to the acceptance of a less than ideal treatment arrangement. If, in addition, these collimators themselves become radioactive, this adds significantly to the problems of accurate treatment.

A serious problem with all neutron therapy facilities at the present time is that the fields are of fixed sizes and shape.



A representative selection of neutron collimators demonstrating that the fields are of fixed sizes and shapes.

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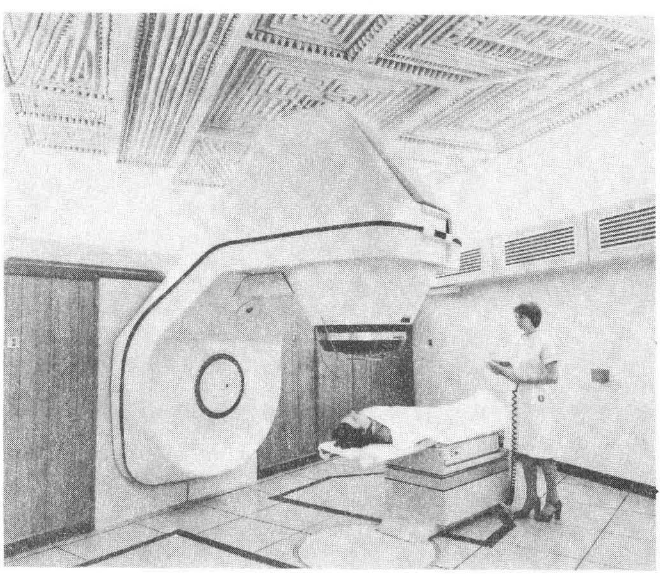
The only way in which this can be modified is by the introduction of inserts. In contrast, modern megavoltage apparatus collimators consist of moveable jaws which provide infinite variations in field size between the physical limits set by the mechanics of the jaws. This allows the choice of the exact field size required for any particular treatment with accurate beam definition. Exact shielding of normal structures from radiation can be carried out precisely. A higher rate of complications which might therefore be seen following neutron treatments may not be the result of any inherent property of neutrons, but simply because of the inferior delivery of dose to the tumour. This problem is aggravated further if there is limited time available for treatments on neutron machines as this can lead to hurried set-ups with even less accurate treatments.

6. The beam should not be fixed in one position.

The great advantage with modern megavoltage apparatus is that beams of radiation may be delivered through 360 degrees and through fields oblique to the long axis of the body. This enables treatment to be directed in whichever way is most appropriate in order to deliver an adequate dose to the tumour whilst at the same time avoiding vital normal structures. In addition, this facility allows the treatment of those patients whose general condition limits their position to be carried out without difficulty.

The fixed horizontal treatment beam which neutron therapy facilities have possessed until recent times, poses many problems in accurate treatment planning and set-up and is a serious obstacle to the conduct of comparative clinical studies. Should only a fixed beam be possible, a vertical beam is preferable.

If treatments are to be fully comparable to those given on megavoltage photon apparatus an iso-centric facility is essential.



A modern isocentric neutron therapy machine.

CONCLUSION

Neutron therapy would appear to offer the possibility of a significant improvement in local cancer control. The work so far carried out suggests that there may be a real advantage for its use in the treatment of advanced cancers and those tumours traditionally regarded as being radio-resistant. This is in spite of using equipment which technically is greatly inferior to that which is routinely available for photon therapy.

Further work is now being undertaken throughout the world investigating the treatment of earlier tumours in order to establish a precise role for neutrons. It is important that this work is carried out with machines comparable with megavoltage apparatus in all the six aspects discussed.

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** DISCUSSION **

M. CHAUDHRI: Last week there was an international meeting at the Hague regarding clinical applications and experience with neutron therapy, at which most of the groups around the world reported their findings. Could you tell us what the general consensus was regarding the success achieved so far?

S. ARNOTT: There were two principle findings from the meeting. One was from a group such as the Hammersmith Hospital, where studies have been carried out for many years. There is no doubt that for the types of tumors I've described – advanced tumors, tumors which are radio-resistant – their results using neutrons are statistically superior to those using x-rays. Most of the other centers have not got sufficient numbers or have not been treating patients for sufficiently long to have got statistically significant results. But there can be no doubt that there are some very interesting results taking place around the world. Our group in Edinborough has been conducting neutron therapy for a much shorter time than has Dr. Mary Catterall in London, and we are certainly achieving the same rate of short-term tumor control.

I would like to point out that most of the treatments so far have been carried out on machines which technically are inferior. If we are really going to produce a form of treatment which is comparable to x-ray therapy, then we must improve the machines which we're using.

G. GORDON: Would a compromise of several angled fixed beams be satisfactory?

S. ARNOTT: Almost anything is better than a fixed horizontal beam. But if you start moving patients during their treatment, there is a danger that the relative position of the tumor within the patient may move such that part of the tumor may be missed for part of the treatment. There is no real alternative to a moveable isocentric treatment machine.

G. GORDON: If the tumor moves within the patient, how is the tumor located just prior to treatment?

S. ARNOTT: The tumor is located in the patient by a combination of clinical examination and detailed radiology and scanning techniques.

J. BURGERJON: What do you consider the optimum energy for a neutron therapy cyclotron?

S. ARNOTT: One has to talk about mean neutron energy. To achieve a depth dose distribution in tissues which is equivalent at least to cobalt, and preferably approaching 4 MV X-rays, one needs a neutron energy of about 18-20 MeV.

W. DAVIES: How do you compare neutron therapy with high energy proton therapy from a clinical point of view?

S. ARNOTT: At the moment we have a lot of experience with neutrons but generally not much with protons. While there are many interesting possibilities in the proton field, some of which are being pursued in the U.S., I feel at this moment in time that neutrons are superior to protons as a practical therapeutic tool.

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