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DEVELOPMENT OF FAST NEUTRON THERAPY WORLDWIDE

Radiobiological, clinical and technical aspects

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Radiobiological data indicate that fast neutrons could bring a benefit in the treatment of some tumour types, and suggest mechanisms through which this benefit could be achieved. However, radiobiology also clearly indicates that there is a need for patient selection as well as for a high-physical selectivity. The main difficulty when interpreting the results of neutron therapy are the poor technical conditions in which the first treatments were applied. This explains why the value and the place of neutron therapy are not universally recognized, although more than 15 000 patients have been treated so far worldwide. There are, however, clinical indications of fast neutrons bringing a benefit for the following tumour sites: salivary glands, paranasal sinuses, soft tissue sarcomas, prostatic adenocarcinomas, palliative treatment of melanoma and rectum. These tumours represent about 10–15% of all patients currently referred to the radiation therapy departments.

When neutron therapy was started in the Hammersmith Hospital in the seventies and a few years later in several other centers, it generated a great deal of interest and hope in the radiotherapeutic community (1–4). In fact, the first attempt at treating cancers with accelerator produced beams of fast neutrons was initiated in 1938, only 6 years after Chadwick's discovery of the particle (5). At that time, there was no scientific rationale for their use other than it was hoped that, relative to their effects on normal tissues, neutrons would be more effective than photons in controlling malignant tumour growth. This pioneering work was to end during the Second World War when the Berkeley cyclotron in California was needed for the war effort. Although a few of the patients were still alive some 30 years later, a great deal of harm was done because of excessive normal tissue damage, especially late damage. As a result, it was recommended by Stone, the principal investigator of the neutron therapy program, that there was no justification for the continuation of neutron therapy.

No further attempt was made until 1966, when the group of the Hammersmith Hospital reconsidered the problem and developed a rationale for fast neutrons (or more generally for high-LET radiation) based on several radiobiological arguments. The most important argument was the observed reduction of the Oxygen Enhancement Ratio (OER) with neutrons compared to photons. It can be summarized as follows:

(1) The existence of hypoxic cells in all (or in most of) malignant tumours;
(2) A specific radioresistance of these hypoxic cells to x-rays, expressed by the Oxygen Enhancement Ratio (OER) which is about 3. The OER is the dose ratio necessary to obtain a given biological effect when irradiation is performed under hypoxic or oxygenated conditions.
(3) From these 2 statements it is apparent that the presence of a small percentage of hypoxic cells (3 times more

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radioresistant to x-rays) makes the tumour definitively radioresistant to x-rays.

(4) Neutrons reduce the OER to about 1.6. To the extent that the hypoxic cells are really the cause of tumour radioresistance, it is then possible to evaluate the therapeutic gain which is the ratio of the OER's for x-rays and neutrons respectively. The therapeutic gain factor (Hypoxic Gain Factor) is thus $3:1.6 = 1.9$.

Two points should be stressed when discussing the rationale for introducing fast neutrons: the hypoxic gain factor of about 1.9 is high and it applies to all (or most of the) tumours since all (or most of them) contain hypoxic cells.

Clinical applications were started at the Hammersmith Hospital after extensive and careful radiobiological experiments. These were justified by the negative conclusions derived from the clinical experience of Stone mentioned above (5). Some of the reasons for the late complications reported by Stone could be explained, e.g. increase of RBE with decreasing dose, higher RBE for late complications compared to early reactions, etc. The radiobiological information progressively accumulated was of great help in designing the therapeutic protocols.

Besides the radiobiological aspects, some of the technical difficulties of the early applications of neutrons should be stressed. Many of the generators produced only low-energy neutron-beams with poor penetration and only fixed horizontal beams were available. In addition, some teams used existing accelerators not designed for medical purposes and often located outside the hospitals. Although these technical shortcomings were recognized, their practical importance was not fully realized since it was expected that the 'radiobiological' therapeutic gain would be large enough to outweigh the technical and physical suboptimal conditions (6, 7).

As far as the clinical results are concerned, after the encouraging results from Hammersmith (1, 8, 9), some conflicting results started to emerge from different centres and serious doubts about the efficacy of fast neutrons were again raised (10–12). It became gradually evident that the outcome of the first neutron therapy studies were biassed by the use of 'suboptimal' neutron beams and that the only way to reach a clear conclusion was to use neutron therapy equipment which would be similar in all aspects to photon isocentric high-energy linear accelerators. It is only in this way that the radiobiological properties of the two beam qualities could be compared unequivocally (13).

In the present review, the radiobiological data relevant to neutron therapy are first presented, followed by the clinical results and the survey of the technological developments in the field of neutron therapy. As far as the clinical results are concerned, some of them will be mentioned only briefly since they are discussed in detail by other authors in these proceedings.

Radiobiological data

The hypoxic cells

As far as the hypoxic cells are concerned, their existence was confirmed in all tumours investigated (14). In contrast, the relevance of the hypoxic cells in relation to tumour radioresistance was questioned after the discovery of the phenomenon of tumour reoxygenation by van Putten & Kallman (15). During the course of a fractionated treatment, some of the hypoxic cells move from the hypoxic to the oxygenated compartment. However, the kinetics of the tumour reoxygenation varies to a large extent from tumour to tumour (16). As indicated in Fig. 1, for rapidly growing, rapidly shrinking tumours, the proportion of hypoxic cells decreases quickly after irradiation and, in a fractionated treatment, they never reach a level where they could become a factor of radioresistance. Reoxygenation does not take place or takes place too slowly in slowly growing and slowly shrinking sarcomas, making the tumour progressively radioresistant. This was the case of the osteosarcoma studied by van Putten, where the percentage of hypoxic cells remained high for several days.

Without entering into detail, it can be assumed today that hypoxic cells do play a major role in the radioresistance of some tumours. In contrast, they do not play any role in other tumours because of efficient reoxygenation, but they probably play 'some' role in other tumour types. This raises the problem of the identification of these different groups of tumours or patients. The importance of patient selection will be discussed again later in this review.

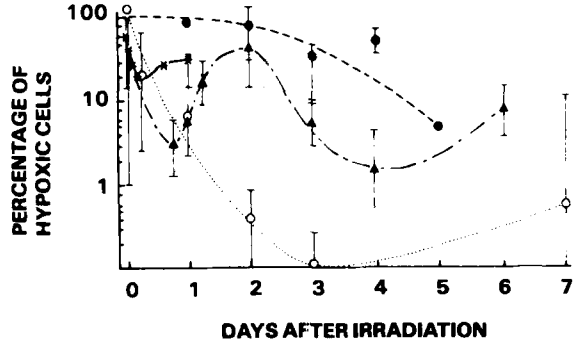

Fig. 1. Tumour reoxygenation after irradiation. In ordinate, the percentage of hypoxic cells is plotted as a function of time (days) after irradiation: –○–for a mouse mammary carcinoma, reoxygenation is rapid and complete: 3 days after irradiation the percentage of hypoxic cells is lower than that seen before irradiation (after Howes); –*–for a transplantable mouse sarcoma, reoxygenation is not complete by 24 h (after Kallman et al.); –▲–for a rat fibrosarcoma RIB5 there is at first a rapid reoxygenation. However, the proportion of hypoxic cells increases again at 2 days and then falls to about 5% at 3 and 4 days (after Thomlinson); –●–for a mouse osteogenic sarcoma reoxygenation is very slow (after van Putten). Comparison of the curves indicates large variations in the time course and extent to tumour reoxygenation from one tumour to another. After Thomlinson (16).

Reduction in the differences in radiosensitivity

When comparing the effects produced by neutrons and x-rays, differences other than a reduction in OER are also observed. The situation could be summarized as follows: with neutrons there is a general reduction in the differences in radiosensitivity between cell populations. For example, Fig. 2 illustrates the reduction in the difference of the radiosensitivity of the cells related to their position in the mitotic cycle (17). Cell populations, synchronized in vitro, are irradiated in different phases of the mitotic cycle. The large differences which are observed with x-ray (low-LET radiation) are progressively but markedly reduced with increasing LET. A reduction in the difference in intrinsic radiosensitivity between cell lines has also been observed (18), although other data suggest that the ranking of radiosensitivity of some cell lines could be altered when x-rays are replaced by fast neutrons (Fig. 3) (19).

Finally, with increasing LET there is a reduction in the role of sublethal lesions. Differences in the capacity of accumulating and repairing sublethal lesions are then of less importance. This implies that the dose per fraction also becomes less critical, which could have some practical advantages e.g. for reducing the number of fractions and/or reducing the overall time for fastly proliferating tumours. It can thus be concluded that all cell populations in all conditions tend to respond in a more similar way to neutrons than to x-rays. This can be logically related to the increase, by a factor of about 100, in the sizes of the individual energy deposits as can be derived from microdosimetric measurements (Fig. 4) (20, 21).

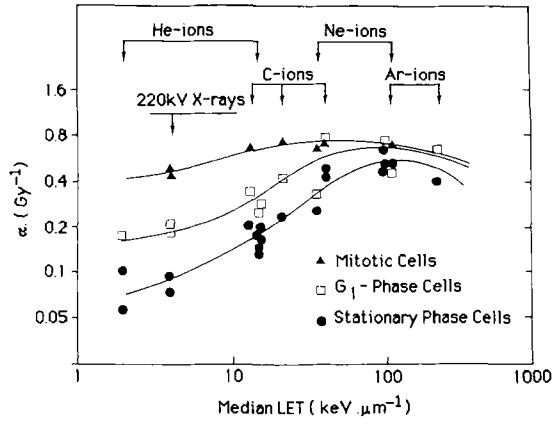

Fig. 2. The differences in cell radiosensitivity related to the position in the mitotic cycle decreases with increasing LET. In ordinate, the cell radiosensitivity is expressed by the parameter α (single-hit inaction coefficient). Synchronized population of Chinese hamster cells are irradiated in mitosis, G_1 phase and stationary phase, with 220 kV x-rays and various beams of charged particles. The α coefficients are plotted as a function of the median LET (in keV · μm^{-1}). After Chapman (17).

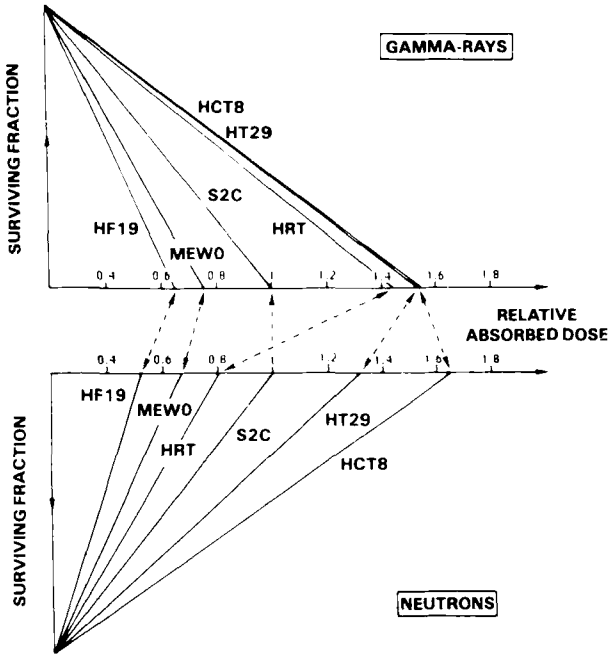

Fig. 3. Comparison of surviving fractions for six cell lines irradiated with ^{60}Co γ-rays and d(50) + Be neutrons. Survival of the six populations has been calculated for a fractionated irradiation given with fractions of 2 Gy (γ-equivalent). The $_{eff}D_0$ values were deduced from the α- and β-coefficients derived from the survival curves observed in vitro. To facilitate the comparison, relative absorbed doses are indicated on the abscissa, the S2C cells being taken as the reference. The variations of radiosensitivity are as important with neutrons as with photons, but the order of radiosensitivities is altered (calculated from the data of Fertil et al. (19)).

Practical conclusions for radiation therapy

Need for proper patient selection. A reduction in the differences of radiosensitivity related to the position of the cells in the mitotic cycle, cell line or repair capacity can be an advantage or a disadvantage depending on the characteristics of the tumours and of the normal tissues at risk. For example, neutrons should not be used for patients in whom, with x-rays, a differential effect selectively protects the normal tissues. However, neutrons may be of advantage in inverse situations when tumour cells are more resistant to x-rays than the normal cell populations (Fig. 5). This stresses the importance of patient selection: an incorrect choice of the radiation quality can worsen the clinical results. More generally, if a subgroup suitable for high-LET radiation cannot be identified, and if the whole group is treated with neutrons, the advantage gained in the subgroup will be diluted or counterbalanced by the worse results obtained in the other subgroups which it would have been better to treat with photons. In practice this could lead to erroneous clinical conclusions as discussed in more detail elsewhere (22).

The importance of physical selectivity. As a result of the reduction in the (radiobiological) differential effect, the therapeutic efficiency of the treatment will depend to a

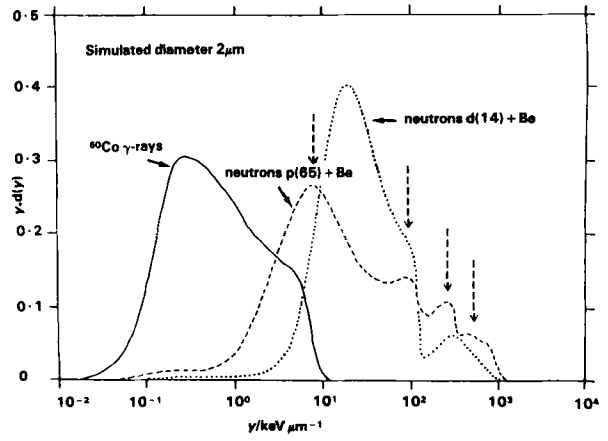

Fig. 4. Comparison of energy depositions after irradiation with fast neutrons and γ-rays. The curves indicate the distributions of individual energy-deposition events in a simulated volume of tissue 2 μm in diameter. The parameter y (lineal energy) represents the energy deposited by a single charged particle traversing the sphere, divided by the mean cord length. The maximum with γ-rays is at 0.3 keV $\cdot$ μm^{-1} and with d(14)+Be neutrons at 20 keV $\cdot$ μm^{-1}. The spectrum for p(65)+Be neutrons shows 4 peaks: the first is at 8 keV $\cdot$ μm^{-1} and corresponds to high energy protons, the second at 100 keV $\cdot$ μm^{-1} corresponds to low energy protons, the third at 300 keV $\cdot$ μm^{-1} is due to α-particles and the last at 700 keV $\cdot$ μm^{-1} is due to recoil nuclei. After Menzel et al. (20) and Pihet et al. (21).

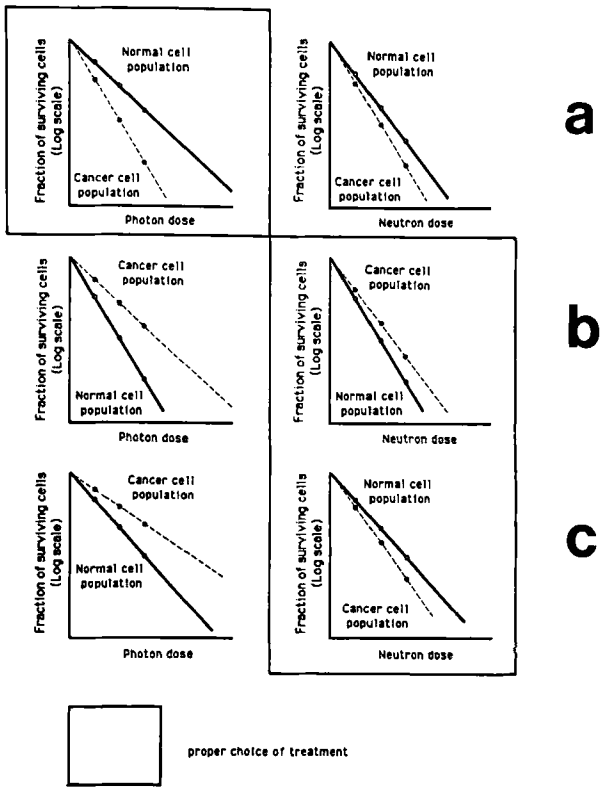

Fig. 5. Importance of patient selection for fast neutron therapy. Three possible clinical situations are considered. In the first, (a), the cancer cells are more sensitive to x-rays than the critical normal cell population, and there is no argument at all for using neutrons which would reduce a favourable differential effect. In the second sitution, (b), neutrons bring a benefit by reducing a difference in radiosensitivity which would selectively protect the cancer cell population. A third more favourable situation is shown, (c), where the relative radiosensitivities are reversed (see text and Fig. 3). It has been assumed in the figure that the survival curves are exponential after fractionated irradiation, i.e. a constant proportion of the cells is killed at each session. However, the exact shape of the cell survival curves is not essential for the present discussion (22).

larger extent on physical selectivity (dose distribution). Thus, physical selectivity is at least as important with high-LET as with low-LET radiations. This is the second important conclusion which is derived from the radiobiological data.

Clinical data

As indicated above, some of the clinical results of fast neutron therapy are discussed in detail by other authors in these proceedings. Therefore, they will be mentioned here very briefly. On the other hand, recent data, especially from the European centres, are reported. They were presented at the 1993 annual meeting of the EORTC Heavy-Particle Therapy Group (European Organization for Research and Treatment of Cancer). This meeting was held in Brussels on 11–13 March 1993.

Salivary gland tumours

Locally extended inoperable salivary gland tumours are the first type of tumours for which the superiority of fast neutrons, compared to conventional low-LET radiations, has been recognized (9, 23–27). All the results of the non-random clinical studies and of the prospective randomized trial overwhelming support the contention that fast neutrons offer a significant advantage in the treatment of inoperable and unresectable primary or recurrent malignant salivary gland tumours. Fast neutron therapy alone should be the treatment of choice for advanced stage salivary gland tumours, and surgery should be limited to cases where there is a high likelihood of achieving a negative surgical margin and where the risk of facial nerve damage is small (28).

Paranasal sinuses

Remarkably good results have also been observed with neutron therapy for locally extended tumours of the paranasal sinuses. In the series treated at the Hammersmith Hospital, 86% (37/43) of the patients showed complete remission and relief of symptoms was noticed in all cases. Thirty percent of the patients survived at 3 years with a 50% local control rate (Table 1) (29). Recently, at the '93 EORTC meeting mentioned above, Errington reported the results obtained at Clatterbridge with p(62) + Be neutrons. Among a total number of 28 patients with

locally advanced malignant tumours of the paranasal sinuses, 26 (93%) had a complete or partial response. The mean duration of the responses was 21 months, and 14 patients (50%) had a complete response. The study is not yet completed, but the median survival was 17 months. The results according to histology are presented in Table 2. Several factors could explain these interesting results, indicating that paranasal sinuses could be a good indication for neutron therapy:

- the superficial location of these tumours (when poorly penetrating beams only are available);
- the diversity of differentiated histology;
- the presence of bone structures, in or near the target volume, which reduces the absorbed dose to the cells located in the osseous cavities (30, 31).

Other head and neck tumours

These tumours are discussed elsewhere in these proceedings. The conflicting results reported from Europe are well known (8, 11). They were obtained with low-energy neutron beams and in suboptimal technical conditions. The same is true for the NIRS data (26) and to the first RTOG trials (32, 33). Only in the last RTOG trial, neutrons were delivered with high-energy, hospital-based cyclotrons (34). It is thus difficult to derive a definitive opinion about the value of fast neutrons. Nevertheless, it seems reasonable to conclude that fast neutrons can bring a benefit in well defined patient series with tumours in the head and neck area, especially locally advanced tumours and fixed metastatic lymph nodes.

Sarcomas of soft tissues, bone and cartilages

Slowly growing, well-differentiated soft tissue sarcomas are treated in most of the neutron therapy centres, mainly because they are often resistant to x-rays and also because of the excellent results reported from Hammersmith (1). When evaluating the results of neutron therapy, comparison with historical series should be made very carefully, since the series may differ histologically, by degree of differentiation, local extent, localization, etc. Furthermore, patient recruitment is influenced by the general treatment policy in a given centre (i.e the relative place of surgery and/or chemotherapy). Therefore, ideally randomized trials are required, but so far have been difficult to achieve for practical reasons.

The largest patient series was treated in Essen. Neutrons only were used first and a 76.5% local control rate was achieved. However, a high percentage of complications was observed (22%), which may be related to poor beam penetration and high skin doses. Therefore, later on, neutrons were no longer used alone, but were applied as a boost: the local control rate was then 61.9% and the complication rate was reduced to 15%. The results of this study are reported in detail by Schmitt et al. (35, 36). A review of the results reported from the different centres (Table 3) indicates an overall local control rate after neutron therapy of 53% for inoperable soft tissue sarcomas. This value is higher than the value of 38% currently observed after low-LET radiation for similar patients series (37).

Taking into account the difficulties in initiating a randomized trial for soft tissue sarcomas, the German Neutron Therapy Group (Chairman M. Wannenmacher) together with the EORTC Heavy Particle Therapy Group, initiated a collaborative study in order to collect all the data from the different participating neutron therapy centres. Strict rules govern data reporting with respect to tumour description, follow-up, treatment technique, dose specification, etc.

The proposed indications of neutron therapy (and/or photon therapy), for low grade soft tissue sarcomas, are presented in Table 4, after Pötter et al. (38).

Conventional radiotherapy generally fails to control bulky primary bone tumours, as appropriate doses in-

Table 1

Results of treatment with 7.5 MeV neutrons for advanced tumours of paranasal sinuses — Histological types, responses and complications

Histological type	Number patients	Complete regression	Recurring	Patients with complications
Squamous	17	14	3	3
Adenoid cystic	11	10	4	4
Adenocarcinoma	8	6	–	1
Transitional cell	5	5	1	2
Undifferentiated	1	1	–	–
Malignant melanoma	1	1	–	–
Total	43	37(86%)	8 (18%)	*10 (23)%

* 2 of these 8 patients who had received previous photon radiotherapy
From Errington (29)

Table 2

Locally advanced malignant tumours of the paranasal sinuses treated with p(62)+Be neutrons at Clatterbridge

Histology	Cause of death				
	Local tumour progression	Local tumour + metastases	Metastases alone	Intercurrent disease only	Total
Squamous cell carcinoma n = 10	3	2	1	3	9
Adenoid cystic n = 10	3	1	1	0	5
Undifferentiated n = 2	0	0	1	0	1
Transitional cell n = 2	2	0	0	0	2
Sarcoma n = 2	0	0	0	0	0
Adenocarcinoma n = 1	0	0	0	1	0
Melanoma n = 1	0	1	0	0	0
Total on study n = 28	8	4	3	4	19

(RD Errington, personal communication, 1993).

Table 3

Review of the local control rates for soft-tissue sarcomas, treated definitively with radiation therapy

Institutions	Number of patients*	local control
		n(%)
Neutrons		
Essen + Heidelberg, 1983	60	31(52%)
Hammersmith, 1987	50	26(52%)
Hamburg, 1987	45	27(60%)
TAMVEC, 1980	29	18(62%)
Fermilaboratory, 1984	26	13(50%)
Seattle, 1986	21	15(71%)**
Louvain-la-Neuve, 1982	19	4(21%)
Amsterdam, 1981	13	8(61%)
NIRS, 1979	12	7(58%)
Edinburgh, 1986	12	5(42%)
MANTA, 1980	10	4(40%)
Overall	297	158(53%)
Photons/electrons		
Tepper & Suit, 1985	51	17(33%)
Duncan & Dewar, 1985	25	5(20%)
McNeer et al., 1968	25	14(56%)
Windeyer et al., 1966	22	13(59%)
Leibel et al., 1983	5	0(%)
Overall	128	49(38%)

* Patients treated de novo or for gross disease after surgery are included but not patients treated postoperatively for microscopic residual disease or for limited macroscopic residual disease.
** Two-year actuarial data
Modified from Laramore et al. (37)

evitably induce osteoradionecrosis. The low neutron kerma in bone reduces the absorbed dose by 25% or more to cells in osseous cavities (30) and allows the application of adequate doses with a reduced probability of late normal bone injury. Hence, differentiated primary bone tumours in adults were part of many clinical neutron programmes. The review of published data indicates that for 88 patients with osteosarcoma treated at different institutions, a persisting local control of 54% (52/97) was achieved (37, 39). Most of these patients had inoperable tumours or refused amputation. An overall local control rate of 21% after photon irradiation is currently reported for similar patient series. However, due to the large treatment volumes and often preceding chemotherapy, a complication rate up to 36% was registered (40). The review of the results reported from the same institutions indicates a persisting local control of differentiated chondrosarcomas after neutron therapy in 49% (25/51) of the patients (37, 39). This value compares well with the 33% (10/30) local control rate achieved after photon irradiation. Debulking surgery followed by appropriate neutron- or neutron-boost irradiation then may become an alternative to ablative or mutilating surgery.

In conclusion, fast neutrons may be considered the best radiation quality for differentiated, slowly growing soft tissue sarcomas, especially locally extended, inoperable or recurrent tumours. A similar conclusion may apply to osteosarcomas and chondrosarcomas.

Table 4

Indications of neutron (and/or photon) radiotherapy for low grade soft tissue sarcoma

Type of surgery	Plane of dissection	Microscopic appearance	Local control after surgery	Indication for radiotherapy	Local control after combined modality
Intracapsular	Within leasion	Tumour at margin	0%	Neutrons (+photons?)	30–50%
Marginal	Within reactive zone —extracapsular	Reactive tissue microsatellite tumour	10–20%	Neutrons (+photons?)	>50%
Wide	Beyond reactive zone through normal tissue within compartment	Normal tissue	50–60%	Photons	90%
Radical	Normal tissue extracompartmental	Normal tissue	80–90%	Photons (rare)	>90%

(Modified after Pötter et al. (38))

Prostatic adenocarcinomas

Prostatic adenocarcinomas, having in general a long doubling time, should be a good indication for neutron therapy taking into account the available radiobiological data (41). In fact, the benefit of neutron therapy was rapidly recognized in several centres, e.g. in Hamburg by Franke (42), in Chiba by Tsunemoto et al. (26), and in Louvain-la-Neuve by Richard et al. (43). However, the most convincing data are the results of two randomized trials, initiated by the RTOG, on locally advanced adenocarcinomas of the prostatic gland (44, 45).

Of course, account must be taken of the slow natural history of prostatic adenocarcinoma and caution is necessary before deriving definitive conclusions. However, the clinical data at present available indicate a significant benefit for fast neutrons (used alone or in mixed schedule?) compared to the current photon irradiation modalities for locally advanced cases. They confirm the selective efficiency of neutrons against slowly growing, well-differentiated tumours, as well as the importance of the physical selectivity when high-LET radiations are used, as could be expected from the radiobiological data. The role of the collimation system on the complication rate is especially illustrative. The clinical data on prostatic adenocarcinoma are reviewed in more detail in another paper in these proceedings.

Inoperable or recurrent rectal carcinoma

Inoperable or recurrent rectal carcinoma appears to be a promising indication for fast neutron therapy (46). Pilot studies were performed in several centers: e.g. Heidelberg and Münster in Germany, Orléans in France and Louvain-la-Neuve in Belgium. The results were discussed and compared at the EORTC meeting in Brussels mentioned above (March 1993). They can be summarized as follows (R. Engenhart, personal communication).

Pain relief appears to be the best criterion to evaluate the response to the treatment. In a group of 90 patients treated in Heidelberg, there was a complete pain relief in 50% of the patients, a good pain relief in 32%, no change in 16% and the situation became worse in 2 cases. In a group of 34 patients treated in Münster, a complete pain relief was achieved in 18% of the patients, a good pain relief in 71% and no change was observed in 11% of the patients. Similar encouraging results were observed in Orléans and Louvain-la-Neuve; differences in scoring criteria could explain some differences in the reported percentages. Fig. 6 from Heidelberg illustrates the variation of the painscore with time.

As far as survival is concerned, the survival rate of a group of 90 patients treated with neutrons in Heidelberg was about 50% at 24 months and 35% at 36 months compared to 30% and 15% respectively for a historical group of 74 patients treated with photons. Fig. 7 compares the survival rates for patient groups treated in Orléans, Heidelberg and Münster. The type of recruitment certainly influences the observed survival rates. Taking into account these encouraging results, a prospective randomized trial has been initiated by the EORTC Heavy-Particle Group in order to evaluate the possible benefit of fast neutrons (alone or used in mixed schedule).

Other localizations

The benefit of neutron therapy, compared to conventional photon therapy, was shown by several authors for other localizations (or tumour types) such as

- melanomas, as palliative treatment for inoperable or metastatic tumours;
- some bronchus carcinomas (non-small cell carcinoma, adenocarcinoma?) and Pancoast tumours (26, 47);
- some grave IV astrocytomas after incomplete surgery (selected groups) (48);
- oesophagus (26).

Of course, more information is needed for these tumours as well as for other tumours such as cervix (49), bladder

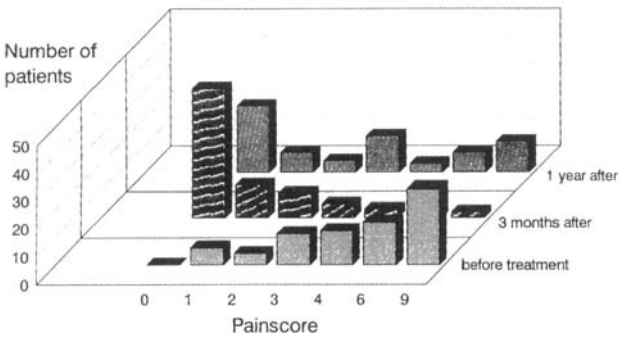

Fig. 6. Evolution with time of the painscore in a group of 90 patients treated with fast neutrons for inoperable or recurrent rectum carcinoma. (R. Engenhart, Heidelberg, personal communication).

(50), pancreatic carcinoma (51) or large breast tumours (13).

Summary of the clinical survey—Indications of fast neutrons

The clinical indications for fast neutrons are summarized in Table 5. They represent about 10–15% of the patients currently referred to the radiation therapy departments. In addition, the tumour types for which neutrons were shown to bring a benefit correspond to a large extent to those predicted by the radiobiological data. Indeed, the most striking results were obtained for well differentiated, slowly growing tumours, often resistant to x-rays as well as to chemotherapy.

Technical developments

The technical conditions, in which fast neutron therapy is applied, have progressively been improved during the last two decades. Briefly, as far as neutron energy is concerned, many of the first patient series were treated

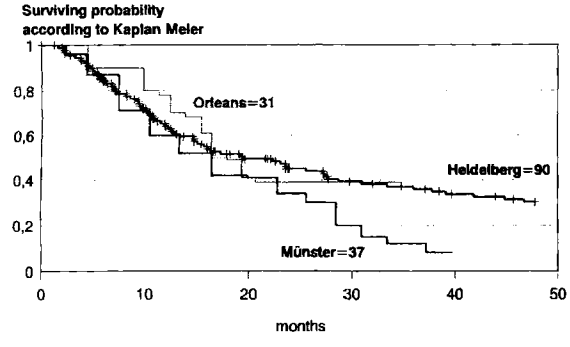

Fig. 7. Survival of patients with inoperable or recurrent rectum carcinoma treated with fast neutrons in Orléans (31 pts), Heidelbert (90 pts) and Münster (37 pts). (R. Engenhart, Heidelberg, personal communication).

Table 5

Clinical indications for neutron therapy (summary)

1. Salivary gland tumours
   locally extended, inoperable or recurrent/well differentiated
2. Paranasal sinuses
   adenocarcinomas, adenoid cystic carcinomas, other histology (?)
3. Some tumours of the head and neck area
   locally extended, metastatic adenopathies
4. Soft tissue sarcomas, osteosarcomas, chondrosarcomas
   especially slowly growing/well differentiated
5. Prostatic adenocarcinomas
   locally extended/well differentiated
6. Rectum carcinomas
   inoperable or recurrent
7. Some non-small-cell bronchus carcinomas
8. Melanomas
   inoperable/recurrent

with low-energy cyclotrons (16 MeV deuterons). Today, neutron beams produced by protons of 45 MeV (or more) are available at several facilities and in 4 centres neutrons are produced by 60 MeV protons, i.e. Clatterbridge, Faure, Fermilab and Louvain-la-Neuve. The depth doses and skin sparing are similar to those of a 10 MV photon linear accelerator.

A fixed horizontal beam was often a practical limitation for patient set-up when physics laboratory-based cyclotrons were used. Today, a rotational gantry is available in several centres, such as Clatterbridge, Detroit, Houston, Faure, Seoul, Seattle, UCLA, etc. Variable collimators are used in Clatterbridge, Faure and UCLA, and multileaf collimators are used in Chiba, Detroit, Louvain-la-Neuve and Seattle (Fig. 8). Of course, the technical problems raised by the beam collimation and the isocentric gantry are far more complex and thus more expensive for neutrons than for photons.

The neutron therapy facilities operational today are listed in Table 6 with their main characteristics. Dosimetric data about neutron beams and protocols for neutron therapy, accepted at the international level, have been published (30, 31). In addition, several intercomparisons were performed between the different neutron therapy centres. These comparisons implied dosimetric, microdosimetric and radiobiological determinations (6, 21, 52).

Discussion and conclusions

Radiobiology

As indicated above, high-LET radiations were introduced in therapy on the basis of radiobiological arguments, and more specifically the existence of hypoxic cells. The bulk of radiobiological data at present available confirm that high-LET radiations indeed can bring a benefit for some tumours types of patient groups. Radiobi-

ology also suggests mechanisms through which this benefit could be achieved:

- the Hypoxic Gain Factor (HGF) related to the reduction in OER;
- the Kinetics Gain Factor (KGF) related to the position of the cells in the mitotic cycle (53);
- less cell repair, and consequently less importance of fraction size. This factor could facilitate the application of concentrated irradiation (i.e. shorter overall time), which has been shown to bring a benefit especially when treating some fast proliferating tumours (short T_{pot}) (54, 55).

Two important practical conclusions can be derived from the radiobiological data. First is the need for proper patient selection and here radiobiology suggests some selection criteria:

- tumours for which hyperbaric oxygen, and hypoxic cell sensitizers were shown to bring a benefit (14, 22);
- in general, slowly growing, well-differentiated tumours (KGF) (41, 55);
- rapidly proliferating tumours (possibility of reducing the overall time).

The last two arguments are to some extent in contradiction. This illustrates the fact that radiobiology can only suggest selection criteria, but that, of course, clinical experience is needed to bring the definitive conclusions. The second important practical conclusion which can be derived from radiobiology is the need for a high physical selectivity, which is at least as important with high- as with low-LET radiations. This is due to the general reduction of the differences in radiosensitivity between cell populations (i.e. less radiobiological differential effect).

Clinical results of fast neutron therapy

The clinical data should be analysed and interpreted bearing in mind the two main conclusions of the radiobiological studies: the need for adequate patient selection and the importance of physical selectivity for high-LET radiations. It is recognized that a great difficulty in the interpretation of the results is due to the 'sub-optimal' treatment conditions in which the neutron treatments were applied, especially for the early patient series. From these results, general conclusions cannot be derived concerning the therapeutic value of neutrons (or high-LET radiations) applied in 'appropriate' technical conditions. Furthermore, the high complication rates reported from several centres have certainly prevented or impaired the development of fast neutron therapy worldwide (10, 11, 24, 56).

In that respect, reports of bad pelvic tolerance after neutron irradiation for cervix, rectum, bladder and prostatic tumours are particularly illustrative. The first patient series were treated using low-energy beams with poor depth doses (12, 24, 49, 57, 58). For these deep seated

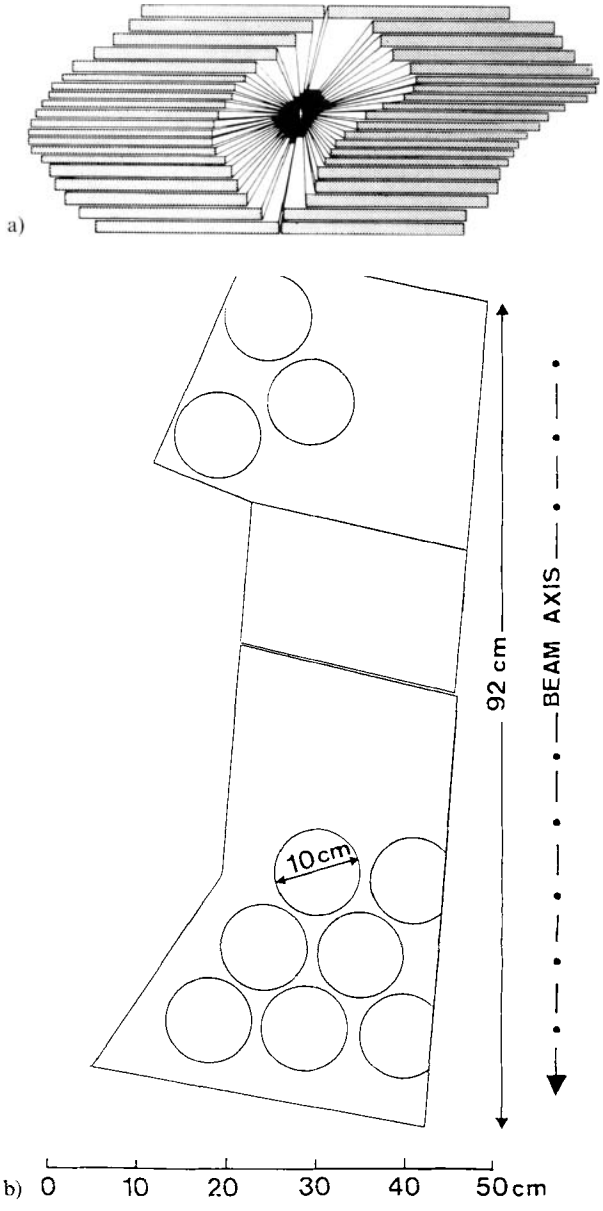

Fig. 8. Variable multi-leaf collimator in neutron therapy. a) Diagram of a variable multi-leaf collimator showing the lower end of the leaves and the collimation surfaces which are all aligned with the proton target (symbolized by the +). Each leaf has its own motor drive and position readout (after Brahme, cited in ref. (31)) and b) Diagram of one of the leaves of the variable multi-leaf collimator recently installed at the cyclotron of Louvain-la-Neuve. The collimator, which has been installed on a vertical neutron beam line, consists of 2 sets of 24 leaves made of steel and borated polyethylene discs (10 cm in ∅). The leaves, calculated for p(65) + Be neutrons, are 92 cm thick. Their width is about 1 cm.

localizations, beam penetration is essential and the obvious conclusion which can be derived is that a poor physical selectivity cannot be compensated by an improved radiobiological therapeutic gain or differential effect related to the beam quality or LET.

The results recently reported from Clatterbridge raise a more complex problem, since the physical characteristics

Table 6

The neutron therapy facilities in the world (October 1993)

Centre		Neutron producing reaction	Comments
Europe			
U.K.	MRC—Clatterbridge	p(62) + Be	Rotational gantry Variable collimator
France	Orléans	p(34) + Be	Vertical beam (horizontal beam planned)
	Nice	p(60) + Be	Vertical beam Multileaf collimator
Belgium	UCL—Louvain-la-Neuve	p(65) + Be	Vertical beam Multileaf collimator (horizontal beam in preparation)
Germany	Hamburg	(d + T)	Rotational gantry
	Heidelberg	(d + T)	Rotational gantry
	Münster	(d + T)	Rotational gantry
	Essen	d(14) + Be	Rotational gantry
	Garching— T.U. Münich	reactor neutrons (av. energy 2 MeV)	Mixed beam
United States			
Texas	M.D. Anderson—Houston	p(42) + Be	Rotational gantry
California	UCLA—Los Angeles	p(46) + Be	Rotational gantry Variable collimator
Washington	Seattle	p(50) + Be	Rotational gantry Multileaf collimator
Illinois	Fermilab	p(66) + Be	Horizontal beam
Michigan	Detroit	d(48) + Be	Isocentric mounting Multi-rod collimator
Asia			
Japan	National Institute of Radiological Sciences (NIRS)—Chiba	d(30) + Be	Vertical beam Multileaf collimator
	Institute for Medical Sciences (IMS)—Tokyo	d(14) + Be	Horizontal beam
Korea	Korea Cancer Center Hospital (KCCH)—Seoul	p(50.5) + Be	Rotational gantry
China	Institute of High Energy Physics—Beijing	p(35) + Be	Proton Linac
Saudi Arabia	King Faisal Hospital—Riyadh	p(26) + Be	Rotational gantry
Africa			
South Africa	National Accelerator Centre (NAC), Faure	p(66) + Be	Rotational gantry variable collimator

of a p(62) + Be neutron beam are similar to that of a 8–10 MV x-ray beam, as far as depth dose, skin sparing and penumbra are concerned. In addition, the Clatterbridge cyclotron is equipped with a rotational gantry and a variable collimator. Nevertheless, the therapeutic benefit actually obtained for bladder, rectum and cervix tumours was considered to be too low and, as a result, treatments of pelvic tumours were stopped.

It was of course important to verify these conclusions, and therefore the pelvic tolerance after neutron irradiation was reviewed in Orléans and Louvain-la-Neuve. The Orléans data are presented in Tables 7–9. For locally extended cervix carcinoma, the complication rate was 12% (15/124). For inoperable or recurrent rectum carcinoma, the complication rate was 7% (8/113). For stages B2, C and D1 prostatic adenocarcinoma, the complication rate was 17% (13/76) (46). These complication rates correspond to grades 2–4 in the EORTC/RTOC scoring system. The possible influence of the AP thickness of the patients on the complication rates was investigated for the 3 localisations treated in Orléans. For the 15 patients with cervix carcinoma who experienced grade 2–4 complications, the average AP thickness was 20.4 cm, whereas it was 20.1 cm for the total group of 124 patients. For the 8 patients with rectum carcinoma who experienced grade 2–4 complications, the average AP thickness was 22.2 cm,

Table 7

Complication rate after neutron therapy for locally extended cervix carcinoma (124 patients, median age 54 years, minimum follow-up 18 months; thereof were 10 patients with grade 2, 4 patients with grade 3 and 1 patient with grade 4 according to the EORTC/RTOG scoring system)

	Complications
Influence of stage	
Stage IIIB (n = 77)	9
Stage IVA (n = 47)	6
Total (n = 124)	15 (12%)
Influence of treatment technique	
Mixed schedule 50 Gy (eq.) + intracavitary therapy	9/81
Mixed schedule 50 Gy (eq.) + boost 15 Gy (eq.) when intracavitary therapy impossible	5/28
Photons of 45 Gy + neutron 20 Gy (eq.)	1/15
Total	15/124 (12%)

CHRO, Orléans (France), March 1993.

Table 8

Complication rate after neutron therapy for inoperable rectum carcinoma (113 patients, median age 64 years, minimum follow-up 18 months; whereof 4 patients with grade 2, 4 patients with grade 3, and none with grade 4 according to the EORTC/RTOG scoring system)

	Complications
Influence of clinical status	
Inoperable (n = 46)	2
Recurrent (n = 67)	6
Total (n = 113)	8 (7%)
Influence of treatment technique	
Photons 45 Gy + neutron boost 20 Gy (eq.)	8/101
Mixed schedule 45 Gy (eq.) + boost 20 Gy (eq.) (3n + 2 ph/week)	0/12
Total	8/113 (7%)

CHRO, Orléans (France), March 1993

compared with 20.6 cm for the total group of 113 patients. For the 13 patients with B2, C and D1 prostatic adenocarcinoma who experienced grade 2–4 complications, the average AP thickness was 21.0 cm, while it was 21.2 cm for the total group of 76 patients. The possible influence of the field sizes on the complication rates was also investigated. For the 15 patients with cervix carcinoma who experienced grade 2–4 complications, the average equivalent square field size was $15.7 \times 15.7\ cm^2$ for the large target volume and $10 \times 10\ cm^2$ for the boost irradiation. For the total group of 124 patients with cervix carcinoma, the corresponding field sizes were $15 \times 15\ cm^2$ and $10.8 \times 10.8\ cm^2$ respectively. For the 8 patients with rectum carcinoma who experienced grade 2–4 complications, the average equivalent square field size was $16.5 \times 16.5\ cm^2$ for the large target volume and $10.5 \times 10.5\ cm^2$ for the boost irradiation. For the total group of 113 patients with rectum carcinoma, the corresponding field sizes were $16.5 \times 16.5\ cm^2$ and $10 \times 10\ cm^2$ respectively. For the 13 patients with B2, C and D1 postatic adenocarcinoma who experienced grade 2–4 complications, the average equivalent square field size was $12.3 \times 12.3\ cm^2$ for the large target volume and $8.1 \times 8.1\ cm^2$ for the boost irradiation. For the total group of 76 patients with prostatic adenocarcinoma, the corresponding field sizes were $13.6 \times 13.6\ cm^2$ and $8 \times 8\ cm^2$ respectively.

Table 9

Complication rate after neutron therapy for locally extended prostatic adenocarcinoma (76 patients, median age 66 years, minimum follow-up 3 years; whereof 10 patients with grade 2, 2 patients with grade 3 and 1 patient with grade 4 according to the EORTC/RTOG scoring system)

	Complications
Influence of stage	
Stage B2 (n = 5)	1
Stage C (n = 42)	9
Stage D1 (n = 29)	3
Total (n = 76)	13 (17%)
Influence of treatment technique	
Mixed schedule 50 Gy (eq.) + boost 16 Gy (eq.)	5/28
Photons 45 Gy + neutron boost 20 Gy (eq.)	8/48
Total	13/76 (17%)

CHRO, Orléans (France), March 1993

In Louvain-la-Neuve, where mixed schedule (3n + 2ph per week) was applied using p(65) + Be neutrons, few complications were observed after pelvic irradiation. In a group of more than 150 patients treated for locally advanced prostatic adenocarcinoma, the early tolerance was excellent and only one late complication, scored grade 3, was observed (urethral stricture in a patient who underwent several surgical procedures) (43, 56). For bladder carcinoma, a recent study confirms that the high-complication rates reported from other centres were not observed (50).

It can be concluded from the Orléans and the Louvain-la-Neuve data that the pelvic tolerance after neutron irradiation is quite acceptable and comparable to the tolerance observed after photon irradiation. When interpreting the discrepancies with the Clatterbridge data, one has to take into account that a dosimetric intercomparison was performed between the 3 centres and showed an excellent agreement and that the microdosimetric characteristics of

the beams were also compared. The possible explanations could then be:

- the proportion of fast neutron dose in the protocols: mixed schedule in Louvain-la-Neuve and Orléans vs neutrons alone in Clatterbridge;
- the fractionation and the size of the neutron dose: 3n + 2ph sessions (5 sessions) per week in Louvain-la-Neuve and Orléans vs 3n sessions per week in Clatterbridge;
- a more frequent use of beam shaping in Louvain-la-Neuve and Orléans, where irregular fields were used routinely.

Technical improvements

The improved technical conditions in which neutron therapy is applied today, at least in some centres, can no longer be compared with those existing in the seventies. Roughly, a similar improvement has been achieved as in the sixties, when 200 kV x-rays were progressively replaced by high-energy linear accelerators.

Progress has been made concerning:

- beam energy: with p(60) + Be neutrons, the same penetration and skin sparing is achieved as with a 10 MV linear accelerator;
- isocentric mounting;
- variable collimation system, and in some centres, a multileaf collimator.

This does not mean that in each neutron therapy centre treatments are applied today in optimal technical conditions comparable to modern photon therapy. However, this situation is recognized by the local medical teams and, to take it into account, the clinical indications for neutron therapy are selected accordingly, sophisticated treatment plans are introduced and mixed-schedule irradiation (or neutron boost) is applied when necessary. However, with the modern (and already existing!) technology, it is possible today to reach with neutrons the same physical selectivity as with photons. It is only under these conditions that the real role of fast neutron therapy can be correctly evaluated.

The investment for a modern neutron therapy facility is approximately 3 times more expensive than for a modern linear accelerator. However, taking into account the reduction of the number of fractions in neutron therapy, the cost of full neutron treatment would then be about 1.5 times the cost of a photon treatment.

Difficulties and remaining problems

From a clinical point of view, one of the most important problems to solve is patient selection. If we are not able to identify the subgroup of patients suitable for neutron therapy, the benefit obtained will be diluted (or even not detectable) and, in addition, counterbalanced by the worse results obtained in other subgroups which would have been better treated with photons. This probably explains, at least in part, some of the discrepancies between the reported results. The choice between low- and high-LET radiations is a radiobiological problem, related to tumour characteristics (and, of course, to the characteristics of the tissues at risk); it is not a machine or accelerator problem. Our capacity of selecting the right patient for the right radiation quality will be improved partly with the progressive build up of clinical experience, and especially with the conclusions of the randomized clinical trials.

However, today much hope is placed in the individual predictive tests, which could allow the therapist to select the optimal treatment modality on the basis of the characteristics of the individual tumours measured in vitro (biopsy). Several types of predictive tests are now being evaluated: intrinsic cell radiosensitivity measured after a test dose (e.g. survival at 2 Gy) in vitro, as well as the number of micronuclei, chromosome aberrations and Premature Chromosome Condensation (PCC). In addition, the potential doubling time, T_{pot}, now appears to be one of the best parameters to estimate the tumour cell profileration capacity. Predictive tests will probably be applied more extensively in radiotherapy, not only to adequately orientate the patients between low- and high-LET radiations, but also to optimize other treatment parameters: dose level, fractionation, combination with drugs, etc.

The second important problem today is patient recruitment. On the assumption (see above and Table 5) that 10–15% of the patients referred today to the radiotherapy departments would require high-LET therapy, one cyclotron would be needed (roughly) to every 10 electron linear accelerators. Under these conditions, only a few large centres will be able to fully use a cyclotron with their own patient recruitment. For centres of moderate or small size, the only solution would be to refer some of their patients to a high-LET therapy facility, but this would imply difficult economical and psychological problems. An alternative is to set up a multicentre collaboration, but past experience has shown neither of these two solutions really works in practice.

In our opinion, the best hope for the future rests in the generalized application of predictive tests. Indeed if, for a given patient, predictive tests (routinely applied) indicate that high-LET radiations would be better, the information would be difficult to ignore and there will be pressure to set up practical conditions for a collaboration between cancer centres.

The recruitment problem is probably the major reason for the slowing down of the neutron therapy programs in the United States and in some European countries. There is, however, a need for high-LET facilities. Taking, for example, the situation in Europe, it is expected that, in the year 2000, about 1 million new cancer cases will be diag-

nosed per year in the EC population. Among them, 60–70% will require radiation therapy (alone or in combination) at one or the other stage of the disease. Assuming that among them, 10–15% will require high-LET therapy (fast neutrons or heavy ions), 60 000–100 000 patients from the EC population per year will need high-LET therapy, and a similar figure can be assumed for North America.

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