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The Trouble with Neutrons

FIFTY YEARS have passed since the first patient was treated with fast neutrons, but this form of therapy is still a matter of bitter dispute. Early experience, as usual, was very exciting but enthusiasm quickly dropped with the first reports of complications, progressively enlarging the gap between advocates and detractors. This is the normal evolution of a non-scientific approach to a medical problem: a period of intense hope is followed by another of deep distrust. Neutrontherapy needs, however, to be judged as any other new and experimental treatment. A panacea was not to be expected and indications allowing for relative advantages and risks must be established.

BIOLOGY

Neutrons, which were first used in the treatment of cancer at the Lawrence Berkeley Laboratory in the 1930s [1], were introduced without a biological or physical rationale, as a potentially useful new treatment modality for otherwise incurable disease. This early experience came to an end with the advent of the Second World War. Subsequently, the potential advantage of fast neutrons over conventional radiation modalties using X- or γ-rays was investigated at the Hammersmith Hospital in the UK. By this time, a radiobiological rationale had emerged: (a) the oxygen effect is less for neutrons than for conventional radiations; (b) repair of sublethal damage is less for neutrons, and cell kill is more efficient; and (c) the variation of cell sensitivity with the phases of the mitotic cycle is less pronounced for neutrons than for photons.

To the extent that hypoxia actually influences the response of human tumour to radiation [2], neutrons would be expected to be beneficial only in tumours with a substantial hypoxic fraction resistant to conventional X-ray therapy. This consituted the major rationale for the development of the neutron programme at Hammersmith. However, two considerations detract from the hypothesis. Firstly, interpatient tumour heterogeneity complicates the identification of subgroups with high levels of hypoxia, rendering optimal patient selection difficult. Secondly, the experimental demonstration of reoxygenation during multifraction irradiation in animals casts doubt on the influence of hypoxia in the conventional radiotherapy. The rationale for neutrons was thus revised.

Cells which have an important recovery capacity (that is cells with a broad shoulder on the survival curve) are selectively spared by conventionally fractionated irradiations, compared to cells which have a limited capacity for recovery. This provides the rationale for fractionation in conventional radiotherapy when normal tissues (particularly late responding normal tissues) recover preferentially from radiation damage in comparison with tumours. Some tumours, however, show a substantial capacity for recovery—for example, some melanomas and some low grade soft tissue sarcomas [3]. They are, therefore, difficult to eradicate with conventional radiations, since attempts to spare normal tissues by fractionation spare to the same extent or an even larger one the irradiated tumour. In such situations, fast neutrons offer a potentially elegant therapeutic approach since they induce more extensive irreparable cellular damage than X-rays. Unfortunately, this damage is not specific for cancer cells but also occurs in normal tissues.

The increased effectiveness of neutrons in cell killing is conventionally expressed as a single parameter, the relative biological effectiveness (RBE). An RBE of 3 means that the same amount of cell kill can be obtained with a neutron dose three times smaller than the corresponding X-ray dose. This is again true for tumours as well as for normal tissues which means that in order not to exceed normal tissue tolerance the total dose in neutrontherapy must be comparatively smaller compared with conventional photon treatment. The difficulty for applying this clinically relates to variation of RBE values, i.e. the dose correcting factors which must be applied. Firstly, the RBE value varies from one normal tissue to another, being generally higher for late effects than for early effects. For example the RBE which can be as high as 5 for the central nervous system [4], is about 2.8–3 for early effects like skin or small bowel [5, 6]. The selection of an average RBE for clinical use thus has to be often arbitrary and the outcome of a compromise between treatment effectiveness and normal tissue sparing. RBE values also depend on the fractionation regimen to which a given tissue is exposed. The difficulty of determining for each clinical situation the appropriate RBE value to be employed explains some of the difficulty of interpreting the results of trials with fast neutrons [7].

With regard to distribution of cells between the various phases of the cell cycle, tumours with a large G_0-G_1 compartment, less sensitive to conventional radiations than actively proliferating tumours, should be particularly appropriate for treatment with neutrons. On the basis of experimental data, Batterman suggested that slowly, well differentiated tumours (with a doubling time > 100 days) were elective indications for neutrontherapy [8]. This coincides with the clinical experience that neutrons appear to be superior for prostate and salivary gland tumours and for soft tissue sarcoma, all relatively slowly growing tumours (cf. below).

The biological properties of any form of radiation are attributed to its pattern of energy deposition. It is believed that high linear energy transfer (LET) radiations are biologically more effective since they deliver a high density of ionisations along their particle tracks, in contrast with low LET radiations which are only sparsely ionising. The LET is simply a measurement of the density of energy deposition per unit path length. In a first approximation, the higher the LET, the bigger the biological efficiency.

An important remark now is that these properties are not peculiar to neutrons, but are shared by all high LET radiations, i.e. but also heavy ions (beams of carbon, neon or argon ions, accelerated to a very high energy). Any discussion about the biological properties of fast neutrons is thus also relevant to these other forms of radiations.

PHYSICS

The biological properties of fast neutrons cannot be dissociated from their physical properties which, unlike those of

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photons, were (and still are) highly variable from centre to centre.

Depth dose distribution of fast neutrons is similar in shape to X- and γ-rays; that is a short build-up region followed by a exponential decrease of the dose in depth. However, only fast neutrons produced by high energy cyclotrons (accelerating protons or deuterons to an energy of at least 40–50 MeV) can achieve depth doses comparable to modern megavoltage X-ray units. Neutron d-T generators and cyclotrons of lower energy (as in the Medical Research Council (MRC) experience) produce beams of inferior quality, more comparable to old 200 kV units or cesium-137 units with a short source-skin distance. The lateral penumbra is also wider with low- than with high-energy neutron beams.

Moreover, most of the early work on neutron therapy was carried out with horizontal or vertical fixed beams of markedly inferior geometry compared with the isocentrically mounted linear accelerators or telecobalt units to which they were compared. It is only recently that the technology of full rotating isocentric neutron beams has reached maturity, but most of the available clinical data derive from trials carried out with fixed beams.

To further complicate the issue it is difficult to compare different neutron facilities in contrast with the high level of standardisation of conventional radiotherapy units. Even when neutrons are produced at similar energies, differences exist between different centres in beam spectra related to the type of target (material, thickness. . .) and in collimation, filtration, etc.

A consequence of this heterogeneity in the physical characteristics of neutron beams is that each beam is associated with its particular biological properties, that is its own RBE, which necessitates a full radiobiological characterisation before the beam is employed in clinical studies. Indeed, RBE values depend also upon neutron energy and vary by a factor of 1.5 between different centres (the higher the energy the lower the RBE) [9]. Even with similar energies there is still variation in beam characteristics as mentioned above. This has always complicated the collaboration between neutrontherapy centres and inhibited the accrual of adequate numbers of patients into cooperative clinical trials. The standardisation of microdosimetric measurements and the development of intercomparison protocols are means of rendering comparison between different facilities easier [10].

Lastly there are also divergences between centres in the measurement and the expression of the neutron dose. Some centres use a correcting factor (the clinical RBE) to express their dose in a photon equivalent gray, whereas others state the neutron dose, but still with some variations in the quotation of the gamma component of the beam (neutron beams always include a small γ component, although to a variable extent) which again makes intercomparisons difficult. This last point should be resolved by the next ICRU (International Commission for Radiation Units and Measurements) report on neutron dosimetry [11].

Hall [12] summarised the combination of optimal features which should be present in order to perform adequate clinical trials with neturons. These include: an adequate dose rate so that the treatment times are not more than a few minutes; depth doses comparable to megavoltage X-ray; an isocentric mounting and location in or near a major medical centre.

CLINICAL ASPECTS

A number of reviews describing the clinical experience have appeared in recent years [13–17]. In a recent paper Schmitt and Wambersie identify tumour types or localisations in which they consider neutrons may have an advantage compared to conventional photon treatment [18]: locally extended salivary gland tumours, paranasal sinuses (adenocarcinomas, adenoid cystic carcinomas), locally extended head and neck metastatic nodes, soft tissue sarcomas, stage C prostate carcinomas and inoperable melanomas. The observations on which these conclusions were based derived in some cases from small series, from uncontrolled studies and from studies in which results were compared with historical or contemporary series published in the literature. This is obviously an inadequate basis on which to conclude that neutrons are either effective or ineffective or whether they are associated with an unacceptable degree of toxicity. Unfortunately the review by Schmitt and Wambersie did not address the issue of normal tissue complications following neutron therapy. The present discussion will only focus on the outcome of randomised trials.

Duncan and his colleagues reported in 1985 the Edinburgh experience in bladder cancer [19]. 113 patients were accrued between 1978 and 1981 in a controlled trial comparing d(15)+Be neutrons with megavoltage X-rays. Because of the poor penetration of the neutron beam, an outdated "cross-fire" technique employed in the orthovoltage era had to be used in the neutron arm (6 convergent fields). Furthermore patients treated by neutrons had to be turned during irradiation sessions because the existing gantry could not rotate through 360°. Analysis of the results showed no benefit for neutrons with respect to local control, but complications were far more frequent and severe. Indeed, the trial was terminated prematurely because of unacceptably high radiation morbidity in the neutron treatment group. Long-term survival also disfavoured the use of fast neutrons in this indication. Careful observation of the isodose distributions shows, however, that a much larger pelvic volume was irradiated in the neutron arm, and especially a much larger volume of small bowel (cf. the volume encompassed by isodose 60 or 70%), as a result of the limited performances of the cyclotron. This in itself is more than enough to explain the higher morbidity in the neutron treatment group.

A phase III RTOG (Radiation Therapy Cooperative Group) study was conducted between 1976 and 1984 in FIGO (Federation Internationale de Gynecologie-Obstetrique) stage III and IVa cervix cancers and reported in 1988 by Maor and colleagues [20]. 156 patients were randomly assigned to receive photons only (50 Gy followed by intracavitary or external boost) or mixed beam radiotherapy (2 fractions neutrons and 3 fractions photons each week, to a total of RBE-adjusted 50 Gy over the same total time followed by a boost). Again none of the neutron facilities can be considered as optimally equipped. In addition, variation in treatment approach arose from the use of different boost techniques, with brachytherapy being delivered in some centres with radium sources and without dosimetry (reported in mgr. hours). Tumour clearance was superior in patients receiving photon therapy (72%) compared with those receiving mixed beam therapy (52%, $P < 0.03$). Local control at 2 years was also better with photons. There was no statistical difference in overall survival, with median times of 2.3 and 1.9 years for photons and mixed beams, respectively ($P = 0.5$). Given the advanced stage of the tumours, the 5 year survival was not so bad for the 2 arms (somewhere between 35 and 45% in the original figure). Although the rate of rectosigmoid complications

was comparable in the 2 treatment groups, the number of small bowel and bladder complications was markedly higher in patients treated with mixed beams. In fact, the rate of major complications in patients receiving only external radiotherapy (photons or mixed beam) was similar in each treatment group (10%). In contrast, patients receiving intracavitary boosts had more complications in the mixed beam arm (27%) compared to the photon arm (10%). As noted above, the intracavitary technique was, however, far from optimum in some centres.

Mixed photon/neutron therapy was compared to photon therapy in advanced head and neck cancers (oral cavity, oropharynx, hypopharynx and larynx) [21]. Five American centres cooperated in the study, with inclusion of 327 patients, between 1977 and 1982. The final report appeared in 1989. Although the overall results failed to demonstrate a significant difference between the 2 treatment groups, subgroup analysis revealed major differences in results for patients presenting with involved lymph nodes compared with those presenting with negative lymph nodes. Patients treated with mixed beam had a better local control if they were node positive and a worse local control if they were node negative at presentation. There was no obvious biological explanation to explain this strange outcome; the authors concluded that the most plausible explanation was "geographical tumour miss" in the node negative patients treated with neutrons (again with horizontal fixed beams of poor general geometry). Complication rates were similar in the 2 groups.

The MRC conducted 2 randomised trials comparing photons with neutrons in advanced head and neck tumours. The Hammersmith concluded that there was a strong advantage for neutrons, with a 76% local control rate, compared to 19% only in the photon treatment group [22]. Various methodological problems have cast doubts about the validity of the comparison, including the unexpectedly poor outcome for patients treated with photons. The trial was repeated in Edinburgh, unfortunately in a group of patients which was not strictly comparable [23]. The latter study failed to demonstrate any advantage for neutrons but reported increased toxicity. The apparent inconsistencies between these 2 head and neck trials formed the basis of a further MRC report [24]. After a careful comparison the conclusion was 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".

Only two randomised trials have reported neutrons to be superior to conventional radiotherapy. An RTOG–MRC cooperative study was conducted between 1980 and 1986 in inoperable salivary gland tumours [25]. A total of 32 patients with recurrent or unresectable tumours were entered in the trial, with 4 participating centres. None of the neutron facilities involved in the study met the criteria of quality defined above, but poor beam penetration was much less critical because of the superficial nature of the tumours. The number of patients accrued was small, but, as the trial progressed, superior results in the neutron arm were so obvious that it was more and more difficult to further include patients in the photon treatment group. The trial was ultimately stopped at the time the difference reached statistical significance. With a follow-up of 2 years, local tumour clearance was achieved in 85% (11/13) of the patients treated with neutrons vs. only 31% (4/13) in the photon group. Two year survival rates were 62 and 25%, respectively. Complications were apparently more frequent after neutron irradiations, but it can be argued that survivors were longer exposed to the risk of developing complications in the neutron arm group. Further evaluation with a longer follow-up is awaited.

Finally, the most frequently cited trial is the RTOG 77-04 protocol comparing mixed neutron/photon treatments with photons in stage C and D1 prostate adenocarcinoma (patients were eligible under 80 years of age). A total of 95 patients were entered between 1977 and 1983, with 91 patients being evaluable for analysis (3 ineligible and 1 refusal). The first report appeared in 1985 [26]. Since that time regular updating reviews confirmed the initial encouraging results for neutrontherapy [27]. In a 1989 report, the 7-year disease specific survival rates were 80% vs. 55% for mixed beams and photons, respectively [28]. Overall survival rates were 64% vs. 25%. The type of therapy appeared to be the most important predictor of both local tumour control and patient survival in a step-wise Cox analysis. However, the trial has been criticised because of the poor results in the photon treatment arm. A possible explanation is that data were analysed by pooling stage C and D1 together. Excluding D1 from the analysis gave a 5-year survival rate of 58% in the photon group which compares well with other RTOG data from previous studies (e.g. protocol 75-06). Even so, the mixed beam treatment gave a superior result when compared with photons. A separate report on neurological complications was published in 1990 [29]. Of 132 patients enrolled into clinical studies on prostate cancer with fast neutrons (including RTOG 77-04), 7 had moderate or severe permanent complications (sciatic nerve or sacral plexus injury), and all 7 were patients who received neutrons or mixed beam therapy. This problem needs to be further carefully followed.

DISCUSSION

On reviewing the available trial data it is clear that, unlike frequently claimed, there has been a substantial effort to evaluate neutrons in clinical practice but that investigators have had to work under adverse conditions. This is underlined by the fact that most of the centres involved in the studies were equipped with fixed (horizontal or less frequently vertical) beams and/or of poor depth penetration. Depth dose distribution, lateral penumbra as well as patient positioning and field alignment were thus constantly less optimal with neutrons than with photons, which systematically led to the irradiation of a larger volume of normal tissues in the neutron treated groups. These technical limitations can likely acount for a significant component of the late morbidity encountered in studies where two treatment modalities of widely differing capabilities to treat deep-seated tumours were placed in direct comparison. Even in the centres with a partially isocentric beam, the low neutron energy imposed the irradiation of a larger normal tissue volume, and to a higher dose, compared to the X-ray treated controls. Patient positioning was also less optimal as the gantry could not rotate 360°. Hence, the outcome of early trials comparing poorly penetrating neutron beams with optimal megavoltage photon therapy was greatly influenced by differences in the physical and geometrical characteristics of the radiation facility. The importance of these technical insufficiences was initially not fully appreciated, since it was believed that the benefit in local control and long term survival would have outweighed the inconvenience of using less performant neutron beams. Unfortunately, but not unexpectedly, the reverse has proved to be true. This was, however, only slowly recognised as the results of the first clinical trials became available.

Nevertheless, it remains true that irrespective of the geometrical and physical characteristics of the neutron beams, normal tissues are comparatively more sensitive to neutrons than to photons, and that the differential effect between tumours and normal tissues is reduced. In this respect, it has probably been an error to use a fixed RBE in all situations, irrespective of the normal tissues involved (except for spinal cord), and above all to derive this RBE from radiobiological experience in acute reacting tissues. This choice directly translated into severe complications for late reacting tissues, rapidly enlarging the gap between believers and non-believers, and further reducing patient referral to neutrontherapy centres.

In essence, a modern neutrontherapy unit needs to be similar in all aspects to a modern isocentric megavoltage unit so that the only variable is the biological property of the neutron beam. In 1990 only a few centres can be considered as optimally equipped with a high energy cyclotron delivering a rotating isocentric neutron beam. Such facilities exist in Clatterbridge (UK), FAURE (South Africa), UCLA (California), M.D. Anderson Hospital (MDAH) (Texas), University of Washington (Seattle) and Seoul (Korea). Two other centres are equipped with a fixed beam but with a variable multileaf collimator. These are Cyclone, with a vertical and a horizontal beam (Louvain-la-Neuve, Belgium) and Medicyc, one vertical beam (Nice, France).

Only 2 trials suggested that fast neutrons could be superior to conventional radiations in tumour control and survival, namely the RTOG 77-04 prostate trial and the RTOG–MRC salivary gland trial. Both of them, however, concluded on the basis of small sample sizes, and the prostate trial still lacks sufficient follow-up, so that neither of them can be considered as conclusive for establishing formal neutron indications in these tumour types.

As a matter of fact, an insufficient number of patients is a constant throughout all neutron trials. For instance, only 146 patients were included in the RTOG trial in cervical cancer [20]. This number was sufficient only to detect a difference of 25% between the two treatment arms with a reasonable type II error (20%). A smaller difference had much less chance to be detected with this sample size. The situation was further complicated by the fact that fewer patients were included in the control treatment arm, which also weakened the power of the study. Smaller control arms are also found in some of the other randomised trials. This aspect is of major importance if one believes that the biological phenomenon at the basis of the possible efficacy of neutrons cannot automatically be expected to lead to very large differences.

A small advantage for neutrons vs. photons, however, would still be of clinical interest since an increase in survival of only 5 to 10% means several hundreds of lives saved in frequent forms of cancer like prostate adenocarcinoma.

The only randomised trial escaping this criticism is the American cooperative trial in unresectable head and neck squamous cell carcinomas [21]. 327 patients were entered with 297 being ultimately analysed (134 photon and 173 mixed beam). As mentioned before, however, results of this study are puzzling and do not allow for definitive conclusions to be drawn. The only positive point was the significantly better locoregional tumour control rate in patients presenting with lymph node metastasis.

In summary, many of the trials did not suggest a difference in tumour control between photons and neutrons, but as the power was generally very low they are mostly inconclusive as to whether neutrons are superior or not (or inferior) in the investigated indications. All is not lost, however, if one believes in the validity of combining similar studies of reasonable quality to achieve an answer that may not be obtained by any one study alone.

These considerations point to the fact that patient recruitment has long been a problem in neutrontherapy centres. Several possible reasons can be identified: some centres were not hospital-based so that available resources in recruitment were limited; the medical use of the cyclotron was only one of many other applications (and had not the highest level of priority); referring hospitals in the neighborhood fell in the non-believer category and did not include patients in trials; some centres were closed each year for long maintenance periods; budgets allocated to neutron research were insufficient leading to serious understaffing in some places; and trial design was deficient, in particular in the definition of appropriate sample sizes (for reasonable type II error level).

It seems, *a posteriori*, that the goals and the means were not properly matched, so that no chance was offered to attain acceptable definitive results. For the future, a sufficient patient accrual will only be secured by those centres which are sufficiently close to the referring hospital and the conventional radiotherapy department in which the medical staff responsible for the neutron facility works. The ideal situation is obviously a hospital-based facility. Finally, trial design must be in accordance with the goal of the studies.

At present only US centres are still involved in cooperative studies. All of them can be considered as well equipped with respect to the quality of the neutron beam. The RTOG has promoted a new trial (protocol 85-23) in prostate cancer which was started in 1986. A total of 178 patients have been randomised between photons and neutrons only (no mixed beam treatments anymore) in 4 centres: Fermilab, UCLA, MDAH and the University of Washington. Of the 178 patients 97 have been included in the latter centre. So far no severe complications have been noted (K. Russell, University of Washington). In the MDAH, 3 out of the first 13 patients included in the trial had severe complications necessitating a colostomy, a very rare event in this centre for patients treated with X-rays (L. Peters, MD Anderson Hospital). The neutron dose had therefore to be adjusted. Problems in choosing an appropriate clinical RBE were also reported by the same institution in another study on advanced breast cancer [30]. Colostomy, due to severe complications in the neutron treatment arm, were also necessary in a few patients from UCLA. Patient acrual stopped at the end of October 1990. The conclusion of this trial and particularly the assessment by the oncologists of its validity will assume a special importance because of the increasing incidence of prostate cancer in Western countries which is now second only to lung cancer as a cause of cancer mortality in men. The number of patients enrolled in this protocol will be sufficient to detect a difference of about 20% between photons and neutrons (i.e. an improvement in survival from 50 to 70%), which seems appropriate given the results of the first prostate trial (RTOG 77-04).

A second RTOG cooperative trial in cervix cancer has been prematurely terminated after the accrual of 60 patients, presumably because of toxicity in the neutron arm. However, the final report has not so far been published. Two other cooperative studies are still ongoing in USA: one in the head and neck and one in non-small cell lung cancer (in patients with good performance status and no weight loss, but presenting with a local bulky lung tumour).

No cooperative randomised trials are currently carried out in Europe since 2 of the 3 centres with high energy neutrons are stopped for improvement of their neutron beam (Nice and Louvain-la-Neuve). Clatterbridge in Liverpool, which has one of the best neutron facilities, has stopped trials involving pelvic irradiation and the only routine indications are salivary gland tumours, sinus, locally advanced prostate cancer (mixed beam) and sarcomas.

CONCLUSION

The combination of the enhanced late reacting tissue sensitivity to neutrons, poor geometry, poor dose distribution and improperly designed trials have all acted against the demonstration of an advantage related to biological characteristics. It should be realised, however, that most of these aspects only slowly emerged as clinical data accumulated. Sadly enough, some severe complications were registered before understanding fully the major importance of this issue. This, combined with the lack of positive results based on undisputed clinical trials, has rapidly broken the initial confidence of the oncological community in this new treatment modality and even led to a very active opposition against the use of neutrons which was crystallised recently in the tremendous political campaign of the whole scientific community in the UK against the setting up of a new neutron generator.

Indications of fast neutrons which seem to be currently accepted include inoperable or recurrent salivary gland tumours and sarcomas. Both of them lack convincing data from randomised trials, but abundant experience exists from non-controlled studies that neutrons do better than conventional X-rays in these indications [17, 18, 31]. The same holds for bulky metastatic neck nodes from head and neck squamous cell cancers. Interesting results have also been communicated in inoperable rectum adenocarcinoma and high grade astrocytoma, using neutrons as boost technique in limited volumes, but again in non-controlled studies [32, 33]. Other indications like locally advanced prostate tumours, unresectable head and neck primary cancers or locally invasive urinary bladder tumours still need optimal clinical evaluation before the oncological community can reach a consensus on whether fast neutrons really offer a benefit over conventional radiotherapy. Normal tissue toxicity will remain a major concern, however, and patients should ideally only be further treated in optimally equipped facilities, i.e. with an isocentric beam of sufficient energy. Beam energy may be lower for head and neck and other superficial indications, but still with optimal geometry in order to limit maximally the extent of the dose delivered to normal tissues.

The whole problem, in the coming years, will be for the responsible medical staff to improve patient selection, and to find optimal fractionation patterns for neutrons. Indeed, there is no *a priori* reason to expect that the best or most effective schedule is the same for neutrons as for X-rays. The contrary is likely to be the case, and different fractionation regimens will be tried, especially smaller numbers of fractions in a shorter time (i.e. accelerated treatment).

We should ask mercy for those already involved in neutron therapy programmes, and offer them all facilities (above all enough patient recruitment) to give the international community a definitive and convincing answer in the coming years. Whether new installations need to be planned in the meantime is less clear, but given the budgets involved, it would probably be wise to wait a little bit longer, before neutrontherapy finds its right place, if it has a place, in the arsenal of anticancer weapons.

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European Winter Oncology Conference (EWOC)

THIS ISSUE of the *EJC* carries a substantial number of papers from this year's European Winter Oncology Conference (EWOC). In essence the papers are short review articles which, while orientated towards the individual author's experience, represent the current status of the field over a wide range of oncology.

The first EWOC Conference was held in 1989, planned as a forum which meets every two years and which constitutes in effect a workshop and an advanced postgraduate course in oncology. Although the emphasis has been on clinical research, there is also the opportunity to present and discuss new developments in basic science. Most areas of oncology have been addressed in the 1989 and 1991 conferences and EWOC will return in January 1993 to many selected topics already covered in 1989. Advances in the field will determine the exact composition of subsequent meetings.

The *EJC*, which is the official journal of the societies under whose auspices EWOC is organised (FECS, ESO and EORTC), was the obvious choice of the organising and scientific committee as an outlet for the wider presentation of papers prepared by the experts participating in the meeting. This is consistent with the aims of the editors of the *EJC*, namely to contribute to the dissemination of knowledge in clinical and experimental oncology. As readers will have noticed since the change of format in May 1990, the *EJC* has carried short invited review papers addressing specific issues and although unsolicited reviews should not be addressed to the *EJC*, those wishing to contribute are able to contact the Editor in Chief to discuss their suggestions. The active participation of readers in submitting original data as fax communications or papers and contributing to the other sections of the journal makes the *EJC* a key forum for scientific exchange over a wide field.

EWOC, a winter event, has been organised as a small scale meeting where the audience and faculty are able to enter into a lively exchange of views in a scientific but relaxed atmosphere. The meetings have already shown their capacity to build strong bonds of collaboration between participants from a wide range of European countries and beyond. The editors of the *EJC* hope that by opening the journal to the contributions of EWOC they will bring a similar learning experience to a much wider audience.

Matti Aapro
Editor, *European Journal of Cancer*