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INTERNATIONAL NUCLEAR DATA COMMITTEE

ATOMIC AND MOLECULAR DATA FOR RADIOTHERAPY

SUMMARY REPORT

First Research Co-ordination Meeting

organized by the
International Atomic Energy Agency

Vienna, 30 January - 2 February 1989

Prepared by

K. Okamoto
IAEA Nuclear Data Section

March 1989

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Abstract

This is the summary report of the First Research Co-ordination Meeting of the IAEA Co-ordinated Research Programme (CRP) on Atomic and Molecular Data for Radiotherapy, convened by the IAEA Nuclear Data Section in Vienna, from 30 January to 2 February 1989. The main objectives of the CRP are to generate, compile and evaluate the important atomic and molecular data relevant to radiotherapy.

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F o r e w o r d

The First Research Co-ordination Meeting (RCM) of the participants of the IAEA Co-ordinated Research Programme (CRP) on Atomic & Molecular Data for Radiotherapy was convened by the IAEA Nuclear Data Section at the IAEA Headquarters in Vienna during the week 30 January - 2 February 1989.

During the meeting the original title was modified to "Atomic and Molecular Data for Radiotherapy" from the original title "Atomic and Molecular Data Needed in Radiotherapy", a proposal which was approved unanimously by all CRP participants.

The main objectives of this CRP are to improve the present deficient status of atomic+ molecular data for radiotherapy, and therefore a comprehensive and co-ordinated effort is needed in the critical evaluation of the existing, but dispersed data and in the measurement and computation of deficient and missing data, with a focus on the more important data required for proton and neutron therapy.

The principal purposes of this first RCM were to present proposed programmes by CRP participants and to exchange views related to the objectives of the CRP and to discuss their contributions to the programme's final report. There were five lectures on selected topics.

The next RCM is planned to be held in January 1991 in Belgium, in series with the other RCM on "Nuclear Data needed for Neutron Therapy".

1. Introduction

The physics data requirements for radiotherapy were for the first time reviewed at an Advisory Group Meeting on Nuclear and Atomic Data for Radiotherapy and related Radiobiology which the Nuclear Data Section convened at the Radiobiological Institute TNO, Rijswijk, the Netherlands, in September 1985. This meeting placed predominant emphasis on the nuclear data requirements and, following its findings and recommendations, the Nuclear Data Section has started an CRP on "Nuclear Data Needed for Neutron Therapy" which is designed to improve the deficient status of neutron cross-sections for the main elements of human tissue in the neutron energy range between 20 and 100 MeV.

The atomic and molecular (A+M) data requirements for radiotherapy turned out to be much more complex than the nuclear data requirements. It was therefore felt that, after the first broad identification of the requirements at the Rijswijk meeting, a more thorough review of the status, availability and important gaps and deficiencies in A+M data for radiotherapy was needed, in order to focus the research under a new CRP on the most important outstanding problems in this field, complementary to the efforts under the CRP on nuclear data for neutron therapy. This review was performed at the recent Advisory Group Meeting on Atomic and Molecular Data for Radiotherapy which the Nuclear Data Section held in Vienna in June 1988. Important contributions to such a review were also provided by the CEC/DOE Workshop on Long-Term Research Needs and Priorities in Microdosimetry for Radiation Protection, May 1985, Toulouse, France, summarized in the report XII/248/86 of the Commission of the European Communities and the U.S. Department of Energy.

The major conclusion from these review activities is, that, in order to improve the deficient data status, a comprehensive and coordinated effort is needed in the critical evaluation of the existing, but dispersed data and in the measurement and computation of deficient and missing data, with a focus on the more important data required for proton and neutron therapy.

2. Organization of the Meeting

The First RCM was chaired by M. Inokuti and L. Toburen. The Agenda of the meeting is listed in Appendix I. The number of participants in this CRP is thirteen from 10 IAEA Member States, 10 of which hold research agreements, three research contracts with the Agency, see Appendix II. Eleven CRP participants, and four participants from the other RCM in the previous week, were present at this meeting, see Appendix III. H. Paretzke, GSF Institute for Radiation Protection, due to an operation, and I. Kaplan, Karpov Institute of Physical Chemistry, Moscow, because of another commitment could not participate. Eleven CRP participants briefly presented their proposed programmes which are summarized in Appendix IV.

The following is the Summary of Observations and Recommendations summarized by M. Inokuti and L.H. Toburen.

SUMMARY OF OBSERVATIONS AND RECOMMENDATIONS

The First Research Co-ordination Meeting on Atomic and Molecular Data for Radiotherapy

Introduction

The background for the present meeting was set forth in the recommendations of the Advisory Group Meeting in June 1988 at the IAEA Headquarters in Vienna, as seen in its Proceedings. What follows is a brief summary of those recommendations, which lead to the formation of the Coordinated Research Programme (CRP).

Scientific scope of the programme

An IAEA Coordinated Research Programme (CRP) on Atomic and Molecular Data for Radiotherapy has been established under the auspices of the IAEA specifically charged with the task of generating, collecting and evaluating the important required physical data relevant to radiation therapy. The CRP is asked to eventually prepare a Handbook type publication entitled "Atomic and Molecular Data for Radiotherapy".

The materials to be considered under the CRP are key substances in the biological cell and key substances used in radiation dosimetry. They are:

Gases: H₂O, H₂, O₂, Ne, Ar, N₂, CO₂, CH₄,
C₃H₈, TE(CH₄), TE(C₃H₈), Air

Solids: C, Be, B, Mg, Al, Si, P, Ca, Fe pure elements
LiF, CaF, A-150 TE plastic, perspex, polyethylene, nylon,
Al₂O₃ and others compounds

Liquids: H₂O

The specific topics of research are summarised below. It is emphasized, that all the listed topics are closely related to each other in research for radiation therapy and are all indispensable.

1. Ionization cross sections

The primary mechanism for energy loss by fast charged particles is ionization of atomic and molecular constituents of the irradiated material. The cross sections for production of secondary electrons of given energies and emission angles are fundamental to the understanding of biological effects, because those secondary electrons cause further processes of excitation and ionization during energy transport.

The process of electron emission is to be reviewed and critically evaluated and additional data are required. Further data are badly needed especially for heavier ions (C and O ions) from a few KeV to a few MeV, which are particularly important in neutron dosimetry, and for faster ions for interpretation of radiobiological effects.

2. Double differential cross-sections

These cross sections are also fundamental for radiation reactions.

2.1. Electron impact

Although many data are available in the USA and Japan, there is a need for a review and a critical evaluation for track structure calculations. Furthermore, additional studies for complete molecular targets (such as larger hydrocarbons and biomolecules) are especially requested.

2.2. Proton impact

Evaluation of the considerable amount of available data is to be done including the establishment of a computer-based data library.

2.3. Heavy ions and neutrals

Only limited data exist for neutral particle impact at very low energies.

Additional emphasis on experimental study is required, especially for interaction of heavy ions with targets of H₂O and hydrocarbon molecules.

3. Charge transfer cross-sections and total ionization cross-sections

A considerable amount of data already exists for charge transfer between light ions and simple atomic and molecular targets. The situation is similar for total ionization cross-sections. These charge transfer cross-sections and electron impact ionization data have been reviewed by Rudd et al.

What is still missing, is to select and compile these data into a complete recommended data file specifically for radiation therapy, using the data and expertise available in the IAEA Nuclear Data Section.

4. Ion-induced excitation and dissociation

For electron impact excitation and dissociation of atoms and simple molecules, a considerable amount of data is available, because of studies relevant to fusion. However, very few data are available for proton and other ion impact.

Further studies on the data for proton and other ion impact are required.

5. Electron collision processes

Interaction of radiation with matter eventually generates free electrons with energies ranging from thermal to very high energies. A large fraction of the primary energy is converted to electron kinetic energy. The interaction of these electrons with matter is of

primary concern in assessing radiation damage occurring in radiation therapy. For the gaseous species of interest in radiotherapy, some data are available but they are never complete. Electron collision processes in the condensed phase are the most important ones, further works in this area should be highly encouraged.

The strongest emphasis should be put on the inaccurate or non-existing data such as for C_3H_8 , and for all species for all processes in the condensed phase. The needed cross-sections are: scattering (total and elastic) cross sections, excitation and dissociation cross-sections and others.

6. Photo-absorption and photo-ionization cross-sections

Absolute, accurate and comprehensive data sets of photo-absorption and photo-ionization cross-sections are of great importance in radiation research. However, in general the experimental data of these cross-sections are not sufficiently accurate, because of experimental difficulties to obtain appropriate photon sources and, because no suitable window materials in the wave length region of VUV-SX are available.

More accurate measurements of photo-absorption and photo-ionization cross-sections and their evaluation, especially for hydrocarbons, molecules containing N and S, polymers, DNA, proteins, ice, clusters and liquids of interest in radiation therapy, are needed.

7. Process of conversion of initial ions and excited neutrals through collisions with other molecules

The ions and excited neutrals formed in primary events or secondary-electron processes change their chemical nature or energy state in collisions with other molecules. These ion-molecule, and neutral-neutral processes are crucial for linking the physics of initial processes with the chemistry of subsequent events in radiolysis. However, actually almost no data are available for such reactions

Systematic determination and compilation of data is to be carried out, with specific emphasis on water and species produced from water.

8. Stopping powers

Stopping powers (STP) determine the average rate of energy loss by primary charged particles such as protons or heavy ions used for therapeutical purposes as impinging particles. The uncertainty in STP and STP ratios directly influences the overall uncertainty in the determination of the total absorbed dose or the kerma. STP in tissues, tissue substitutes, or counting gases may be derived using the Bragg's additivity rule, taking available STP tables for different types of ions over a large range of elemental materials and energies. However, the Bragg's rule is known to be a poor approximation due to chemical binding effects especially for materials with low-Z constituents and for solid compounds at low energy near and below the stopping power maximum.

Critical re-examination and compilation of stopping powers for particles and materials of interest in radiation therapy, particularly for lower charged particle energies and materials with low - Z constituents is therefore urgently required.

9. Initial yields of ions and excited states and electron degradation spectra

Ionization yields in gases and the related quantity "average energy to produce an ion pair" (W-values) are important because of the extensive uses of gas cavity chambers for dosimetry in radiotherapy. Uncertainties in these average W-values directly influence the overall uncertainties in measured Kerma.

Precise total and differential W-values, and evaluation of their average values for different types of secondaries, especially for C₃H₈ and TE(C₃H₈) gases are needed.

10. Track-structure Quantities

Track-structure quantities (microdosimetric spectra, radiation dose distribution, charged particle track simulation) supply the necessary information on the spatial distribution of energy transfer of the critical biological structures. A comprehensive compilation of available results exists but is not well known to the users and also, more experimental and theoretical results are currently becoming available.

Critical review of these available data and their compilation in user-oriented form are required.

Summary of Presentation

The First RCM was chaired by M. Inokuti, with L.H. Toburen serving as co-chairman.

All the participants of the CRP presented short reports on current activities and on planned contributions to the programme's final report. The topics included all areas of research pertinent to the goal of the CRP, i.e., cross sections for charged particle interactions with atoms, molecules, and condensed matter, stopping powers of materials, analysis of electron transport leading to initial products, their conversion through thermal collisions with other molecules, and finally the relation of these early physical processes with later chemical and biological effects of ionizing radiations on various matters of importance to radiation therapy and radiation biophysics.

In addition to the short reports, five lectures on selected topics were presented:

A. Wambersie: The future of high-LET radiation in cancer therapy - Justification of the heavy-ion therapy programme. (The paper, especially prepared for this RCM is attached in this report.)

D.T. Goodhead: Analysis of the role of radiation quality in determining biological effectiveness.

M.J. Berger: Stopping powers for protons and alpha particles.

L. Sanche: Electron phase of condensed materials.

M. Inokuti: Subexcitation electrons.

These lectures treated the current status of each topic at a high scientific level and in great technical detail. Thus, they served for the intended aim of having the CRP participants share the advanced knowledge necessary for scientific collaboration.

The latter half of the meeting was devoted to extensive discussions, in both plenary sessions and two working groups (one led by H. Paul and the other by L.H. Toburen), on the formulation of an outline of the final report of the CRP and on a schedule of work toward this goal. The result is seen in the following.

Tentative outline of a Final Report

The tentative outline of a Final Report as one of IAEA Technical Report Series is as follows:

Preface

1. Development of Charged-Particle Therapy and Requirements for Atomic and Molecular Data (15 pages*)

Wambersie **, Goodhead

2. Ionization Cross Sections for Charged Particles (80 pages*)

Toburen**, Inokuti, Paretzke, (Rudd)***

This chapter will treat total cross sections, single and double differential cross sections for charged particles. (However, the total ionization cross sections for electrons are covered in Chapter 3). This chapter will also include charge transfer and dissociative ionization.

3. Electron Collision Cross Sections (65 pages*)

Märk**

This chapter will treat electron collisions with single atoms and molecules. Processes discussed include ionization, excitation, electron attachment, and elastic scattering.

4. Low-Energy Electron Interactions with Condensed Matter (35 pages*)

Sanche** , Hatano, Märk

This chapter treats dense gases, clusters, liquids, and solids.

5. Photoabsorption, Photoionization, and Photodissociation (30 pages*)

Hatano**

This chapter treats primarily single atoms and molecules, and photon energies up to a few keV.

6. Processes of Conversion of Initial Ions and Excited Species in Collisions with Other Molecules (40 pages*)

Herman** , Hatano, Sanche, Märk

This chapter treats gas phase, clusters, and condensed phase, rates of reactions involving positive and negative ions and excited neutral species, as well as data on energetics, will be included.

7. Stopping Powers, Ranges and Straggling (90 pages*)

Paul** , Srdoc, Berger, Terrissol, Dietze, (Bichsel)***

This chapter treats electrons, protons, alpha particles, and heavier ions.

8. Initial Yields of Ions and Excited Species (60 pages*)

Srdoc** , Inokuti, Paretzke, Berger, (Waibel)***, (Grosswendt)***

This chapter treats initial yields of species produced immediately following energy transport. Quantities discussed include W values, G values, Fano factors, and electron degradation spectra.

9. Track Structure Quantities (50 pages*)

Paretzke** , Terrissol, Goodhead, Kaplan

This chapter presents a survey of track-structure calculations including intercomparison of work by various groups, e.g., Ito (Institute of Medical Sciences, Tokyo), Zaider (Columbia University), Wright (Oak Ridge National Laboratory), and Miller (Pacific Northwest Laboratory), in addition to the chapter authors.

10. Interaction Cross Sections for High-Energy Photons and Electrons (tentative title) (30 pages*)

Berger** , (Seltzer)***, (Hubbell)***

This chapter will discuss recent advances in theoretical calculations of the cross sections, needed for improved dosimetry.

11. Concluding Remarks (10 pages*)

Inokuti**

This chapter presents additional remarks including a list of unsolved problems and areas for suggested research.

Total estimated pages: 500 pages

* Estimated pages

** The underline indicates the leading author of each chapter

*** The parentheses indicate potential special consultants or collaborators

The following schedule of work of the CRP on Atomic and Molecular Data Needed in Radiotherapy was agreed among participants.

1. 30 Jan. 1990 Send introduction to every chapter to NDS (Okamoto)
2. 30 Oct. 1990 Send drafts of chapters to co-authors and other participants of related chapters.
3. Jan. 1991 Second meeting at Brussels, with complete drafts of all chapters. The meeting will include a working session devoted to the reading of the drafts.
4. 1992 or 1993 3rd and Final Meeting, to agree on the final manuscript
5. 1993 or 1994 Publication of the Final Report by IAEA

Recommendations

1. A. Wambersie graciously invited the participants to hold the Second Meeting of this CRP in Brussels early in 1991. There was a definite consensus among all the participants to accept the invitation. At the Second Meeting, all participants will submit preliminary drafts of their contributions to the final report, for a full discussion of their contents. At the Third and Final Meeting to be held in 1992 or 1993, the full text of the final report will be determined. It is therefore recommended that the IAEA-NDS make plans accordingly.
2. There was unanimous agreement that the highest priority in preparing the final report was that it be of the highest scientific quality. This is required if it is to be useful for the readership, which will include not only practitioners of radiotherapy, but also the frontier researchers who produce relevant atomic and molecular data. It is fully recognized that the preparation of a document for such a wide scope of audience is not straightforward, but the present CRP will be truly significant only when it can provide a balanced summary of the status of atomic and molecular data and also identify areas of need for further original research. It is therefore recommended that the IAEA-NDS recognize the high priority to be placed on the scientific quality.
3. As a consequence of the emphasis on the scientific quality, efforts will be devoted primarily to the scientific content rather than to the form of its presentation. Depending upon the nature of the data, they may be presented in words, graphs, tables, mathematical formulas, or computer-accessible media such as disks and softwares. It was especially encouraged that the computer-accessible media be used to present a large volume of data in a form readily usable by the large range of the intended audience of the final report.
4. It was agreed that a slight change of the CRP title into Atomic and Molecular Data for Radiotherapy be recommended. The replacement of "needed in" with "for" will shorten the title, and will imply a slightly broader scope of intended work. It was also agreed that utmost care is necessary in the use of terms such as "heavy ions" vs. "light ions" and "high energy" vs. "low energy", to prevent

misunderstanding. Upon the preparation of the final document, efforts will be devoted to define these terms as clearly as possible in each context of discussion.

5. Because the scope of the final report will be extremely broad and because the thirteen official participants of the CRP will be insufficient to discuss all the areas of coverage at the desirable depth, it will be necessary for the CRP participants to draw on knowledge and expertise of their associates. In that event, these associates should receive proper authorization and credit for their work. One way to accomplish this will be for the IAEA-NDS to write letters to these individuals asking for their assistance (at no cost to the IAEA, a point that need not be explicitly stated).

In other circumstances, the CRP will be greatly strengthened by contributions from external experts. It is recommended that one or two of them be invited to attend the next meeting and be asked to contribute to the preparation of the final report. It is therefore recommended that the IAEA-NDS consider the possibility of obtaining services from such individuals, perhaps in the status of special consultants.

THE FUTURE OF HIGH-LET RADIATION IN CANCER THERAPY. JUSTIFICATION OF THE HEAVY-ION THERAPY PROGRAMMES

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Abstract

The Future of High-LET Radiation in Cancer Therapy. Justification of the Heavy-Ion Therapy Programmes.

André Wambersie.

Control of the primary tumour remains one of the main challenges in cancer therapy, and in that respect, introduction of new types of ionizing radiations is a promising approach in radiation therapy. Particle beams, such as protons or helium ions (low-LET beams), aim at improving the physical selectivity of the irradiation. On the other hand, with these radiations, no benefit has to be expected as far as radiobiology is concerned, since they stay in the field of low-LET radiations. The clinical benefit of using proton or helium ion beams has been demonstrated for several tumour types or sites such as uveal melanomas, chordomas or chondrosarcomas of the base of the skull, paraspinal tumours.

As far as high-LET radiations are concerned, they produce different biological effects compared to conventional X-rays, from which a potential therapeutic gain could be expected. Historically, the rationale for introducing high-LET radiation (in fact fast neutrons) was a reduction in OER. However with high LET radiations, there is also evidence for a reduction in the differences in radiosensitivity related to cell cycle phase, to cell line, or a reduced importance of repair phenomena. In these conditions, all cell populations, in all situations, tend to respond in a more similar way when exposed to high-LET, as compared to low-LET radiations. This can bring an advantage -or a disadvantage- depending on the tumour characteristics and of the normal tissues at risk. This in turn raises the crucial problem of patient selection.

As far as the clinical data are concerned, fast neutrons were found to be superior to photons in the treatment of salivary gland tumours (overall local control rate 67 % vs 24 %), prostatic adenocarcinomas (local control rate 77 % vs 31 %, randomized trial), and some types of sarcomas (overall local control rate 53 % vs 38 %).

Heavy ions combine the advantages of a high physical selectivity (similar to protons) and the potential advantage of high-LET for some types of tumours. The clinical indications for heavy ions would be those tumour types for which high-LET were already shown to be useful (i.e. the previous fast neutron experience) and those sites which raise difficult technical problems. The available clinical experience with fast neutrons and protons justifies the heavy-ion therapy programs. However their cost and complexity require an international collaboration. Besides the US LIBRA project and the Japanese HIMAC program, there are 2 heavy-ion therapy projects in Europe : at the GSI-Darmstadt in Germany and the EULIMA (EUropean Light Ion Medical Accelerator) project.

Introduction

Control of the primary tumour remains one of the main challenges in cancer therapy, and in that respect, the replacement of conventional X or γ rays by other types of ionizing radiations is one of the most promising approaches.

When discussing the potential value of non-conventional types of radiations, one has to distinguish :

- particle beams which only improve the physical selectivity of the irradiation, i.e. the dose distribution (e.g. proton beams or helium ion beams);
- high-LET radiations which produce different types of biological effects, and which aim at improving the differential effect between tumour and normal tissues (e.g. : fast neutrons);
- the two approaches can be combined and one could seek after a high physical selectivity with high-LET radiation (e.g.: heavy ions).

A. Improvement of the physical selectivity with proton and helium ion beams

Historically, the major improvement in the efficiency of radiation therapy was the replacement of conventional X-rays (200 kV X-rays) by high-energy photons or electrons. The clinical benefit was rapidly evident for all, or for the majority of the patients. This illustrates the importance of the physical selectivity in radiation therapy.

We are now close to make a further step : the introduction of proton beams. The characteristics of the proton beams make them superior to high-energy photons from the point of view of the physical selectivity. On the other hand, no advantage has to be expected from the biological point of view : for the high energy required to the protons in external irradiation, we stay in the field of low-LET radiations. For the present discussion, we can assume that helium ion beams are similar to proton beams.

The clinical benefit of proton beams has been demonstrated for several well selected tumour types or sites for which a physical selectivity is essential. The best example is the uveal melanoma, which has been treated since many years by proton beams at the Harvard cyclotron [1]. More than 1 000 patients have been treated between 1974 and December 1986 : a local control rate of 96-98 % and a survival of 80 % were reported (H.D. Suit in [37]. These results compare well with those reported from Berkeley, where the recurrence rate for patients treated with helium ions was 4 % (J.R. Castro in [38]).

An active program (OPTIS) is also carried out at the PSI-Villigen in Switzerland, where 462 patients were treated up to October 1988 (Fig. 1). Survivals at 2 and 4 years of 95 % and 88 % respectively were reported (L. Zografos in [37]).

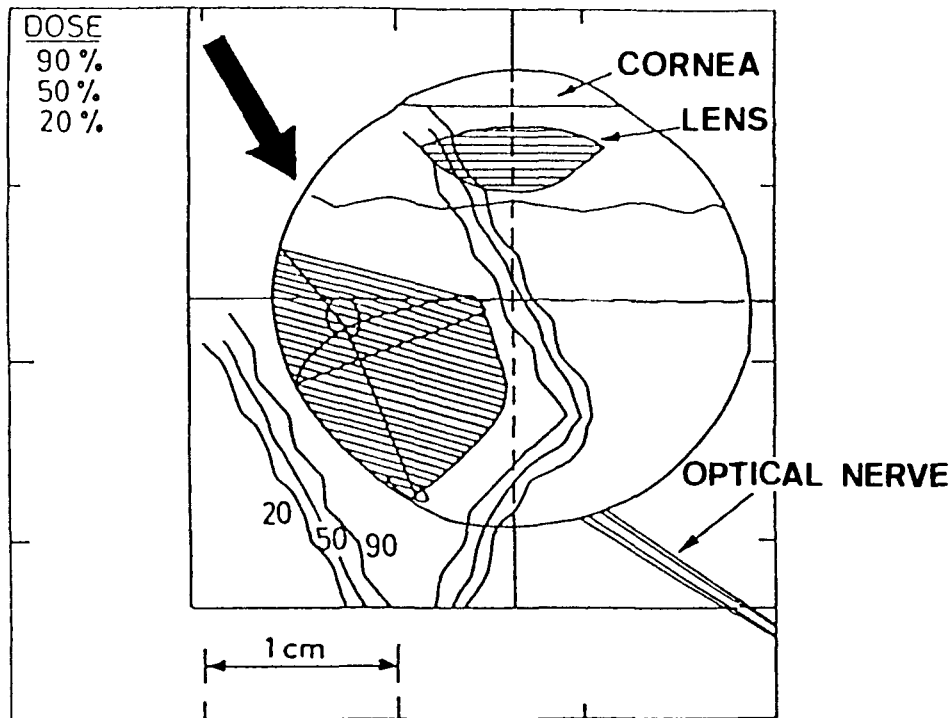


Figure 1

Protontherapy of uveal melanoma. Dose distribution for 60 MeV proton beam; the Bragg peak has been spread out by modulating the energy from 0 to 46 MeV. The tumour (hatched area), as well as some normal structures (cornea, lens, optic nerve) are indicated. The thick arrow corresponds to the beam axis and the 90 %, 50 % and 20 % isodoses are drawn. Proton beams allow one to achieve a homogeneous irradiation of the target volume with a reasonable sparing of the normal tissues. However, an accurate patient positioning is required.

(Courtesy Ch. Perret, PSI - Villigen, cited in [31])

In addition, at least 4 proton therapy programmes for uveal melanoma are in preparation in Europe : in Uppsala - Sweden, Clatterbridge - United Kingdom, Nice - France, and Louvain-la-Neuve - Belgium. For the three last ones, proton therapy is planned with the cyclotrons currently used for fast neutron therapy [32].

Besides uveal melanoma, there are other localisations where the high physical selectivity of the proton beams can be fully exploited : radioresistant tumours close to critical organs such as chordomas or chondrosarcomas of the base of the skull, and paraspinal tumours. At the Harvard cyclotron with protons, local control rates of 82 % and 63 % were reported at 5 and 10 years respectively (H.D. Suit in [37]). A local control rate of 70 % for chordomas, chondrosarcomas and meningiomas was reported from Berkeley after helium ion treatment (J.R. Castro in [38]).

In addition, there is an increasing number of new projects which aim at treating with protons many other tumour types, and larger proportions of patients (Table I). As a matter of fact, since an improved physical selectivity is, in itself, always a benefit, all photon patients could be, in principle, potential candidates for proton treatment.

TABLE I

CHARGED-PARTICLE BIOMEDICAL ACCELERATOR FACILITIES (Excluding π^- facilities)						
A. Programs with accrued patients:	Ion	Energy (MeV/ μm)	Accelerator type	Date of first therapy	Current patient total	Date of total
184", LBL, Berkeley (switched to He, 1957)	H	730	synchrocyclotron	1955	30	1957
184", LBL (programs moved to Bevatron, 1/88)	He	231	synchrocyclotron	1957	1998 *	1/88
Bevatron, LBL, Berkeley	He	70-230	synchrotron	1988	16 **	2/88
GWU, Uppsala, Sweden (see below for upgrade)	H	185	synchrocyclotron	1957	73	1976
Harvard Cyclotron Laboratory/MGH	H	160	cyclotron	1961	4300	6/87
ITEP, Moscow, USSR	H	70-200	synchrotron	1965	1359	10/87
JINR, Dubna, USSR (see below for upgrade)	H	↓80-200	synchrocyclotron	1967	84	1977
LINPH, Gatchina, USSR	H	1000	synchrocyclotron	1975	560	10/87
NIRS, Chiba, Japan	H	70,90	cyclotron	1979	≈30	8/86
PARMS, KEK, Tsukuba, Japan	H	↓250	synchrotron	1983	67	1987
PSI, Villigen, Switzerland	H	100	cyclotron	1984	429	5/88
BEVALAC LBL, Berkeley (cancer treatment)	Ne,Si	≤670	synchrotron	1975	296	2/88
World total patients treated =					9 242	

* 836 radiation therapy, 292 AVM, 870 pituitary, etc...

** 6 radiation therapy, 10 AVM

↓ Clinical-energy beams are obtained by degrading higher-energy beams.

TABLE I (continued)

CHARGED-PARTICLE BIOMEDICAL ACCELERATOR FACILITIES (Excluding π^- facilities)				
B. Facilities under construction/ development :	Ion	Energy (MeV/ μ m)	Accelerator type	Status
<u>Loma Linda, California</u>	H	70-250	synchrotron	Tx the first patient in 1990
<u>NIRS, Chiba, Japan</u>	He-Ar	800	synchrotron	Tx the first patient in 1993
NAC, Faure, South Africa	H	65,200	cyclotron	Designing a medical beam line
GWI, Uppsala, Sweden	H	45,200	cyclotron	Upgraded facility ready for therapy
GWI, Uppsala, Sweden	Ne	20	cyclotron	For biology experiments only
JINR, Dubna, USSR	H	200	synchrocyclotron	Reconstructed and operational in 1987
IPCR, Tokyo, Japan	H,He	210,135	cyclotron	To be completed in 1989
Orsay, France	H	200	synchrocyclotron	Testing for a medical beam line
TRIUMF, Vancouver, Canada	H	150	cyclotron	Developing medical facility
UCL, Louvain-la-Neuve, Belgium	H	90	cyclotron	Tx the first patient in 1990
IHP, Beijing, China	H	70	cyclotron	
MRC, Clatterbridge, UK	H	62	cyclotron	Building a medical beam line
MEDICYC, Nice, France	H	60	cyclotron	Plans to develop a medical beam line

Hospital-based dedicated medical accelerator facility

TABLE I (continued)

CHARGED-PARTICLE BIOMEDICAL ACCELERATOR FACILITIES (Excluding π^- facilities)				
C. Planned facilities	Ion	Energy (MeV μm)	Accelerator type	Status
<u>Mass General Hospital, Boston</u>	H	250	synchrotron	Conceptual design
<u>Beth Israel, New York City</u>	H	250		Conceptual design
<u>Rush-Presbyterian-St. Luke's Medical Center, Chicago</u>	H			Feasibility study
<u>Tsukuba, Japan</u>	H	230	cyclotron	Conceptual design
<u>Osaka, Japan</u>	H	250	cyclotron	Conceptual design
<u>BEVALAC upgrade, Berkeley</u>	H-U	≤ 2000	synchrotron	LBL's first priority
<u>LIBRA, Oakland, CA</u>	He-Ne	500	synchrotron	Conceptual design
<u>EULIMA (EUropean Light Ion Medical Accelerator)</u>	He-Ne	≤ 400		Conceptual design
<u>GSI, Darmstadt, Germany</u>	H-U		synchrotron	Plans to build a medical beam line
<u>ITEP, Moscow, USSR</u>	Heavy ions		synchrotron	Upgrade
<u>Tokai, Japan</u>	He-U	≈ 135		Conceptual design

Hospital-based dedicated medical accelerator facility

After B. Larsson in [38]

Prostatic adenocarcinomas, soft tissue sarcomas, some head and neck and rectal tumours are treated with protons at the Harvard cyclotron [1]. In Japan, 250 MeV protons are used at the University of Tsukuba for different localisations, including deep seated tumours (T. Kitagawa in [38]. The Swedish and Russian proton therapy programmes have been described [24]. An ambitious therapy programmes using 250 MeV protons is in preparation at he PSI in Villigen [7]. In Orsay also, a proton therapy programme using a 200 MeV synchrocyclotron is in preparation (J. Dutreix, personal communication).

However, one of the most impressive projects is probably the Loma Linda project at Los Angeles. A variable energy synchrotron (70-250 MeV), and 3 treatment rooms with isocentric rotating gantry, will be the "core" of a large oncology department. An additional horizontal fixed beam will be reserved for eye and brain irradiation. The facility is scheduled for completion by the end of 1989; once all treatment rooms will be fully operational, the centre is expected to have a capacity of 1 000 new proton beam patients per year [29]. This kind of project really aims at systematically substituting proton to photon beams; it raises a least 3 types of problems :

- 1) to what extent will the clinical benefit justify the increased cost and efforts involved;
- 2) such program will imply, in a more or less near future, a redefinition of the radiotherapy network, and a progressive replacement of several small photon therapy units (or departments) by huge proton therapy facilities;
- 3) finally, the benefit of the high physical selectivity of the proton beams will be fully exploited only to the extent that the accuracy in patient-beam positioning and in dosimetry would reach the same level as with photons. The proton beam generators should also be as reliable as the modern linear accelerators.

It is at present the task (and to some extent the duty) of the teams who have access to high-energy cyclotrons to provide a clear, and quick, response to that problem. It would be indeed a significant improvement to be able to deliver high-doses (60-70 Gy) to bronchus or oesophagus tumours, or to treat a Hodgkin patient, with a (nearly) full sparing of the spinal cord.

B. The differential effect and the potential advantage of neutrons and high-LET radiations

1. Radiobiological considerations

Historically, high-LET radiations (fast neutrons) were introduced in therapy because of the existence of hypoxic cells and the reduction in OER when increasing LET. However, high-LET radiations exhibit other differences in their biological properties, when compared to low-LET radiations :

- a reduction in the differences in radiosensitivity from cell line to cell line (i.e. "intrinsic radiosensitivity") (Fig. 2) [2]. On the other hand, Fertil et al. [15]

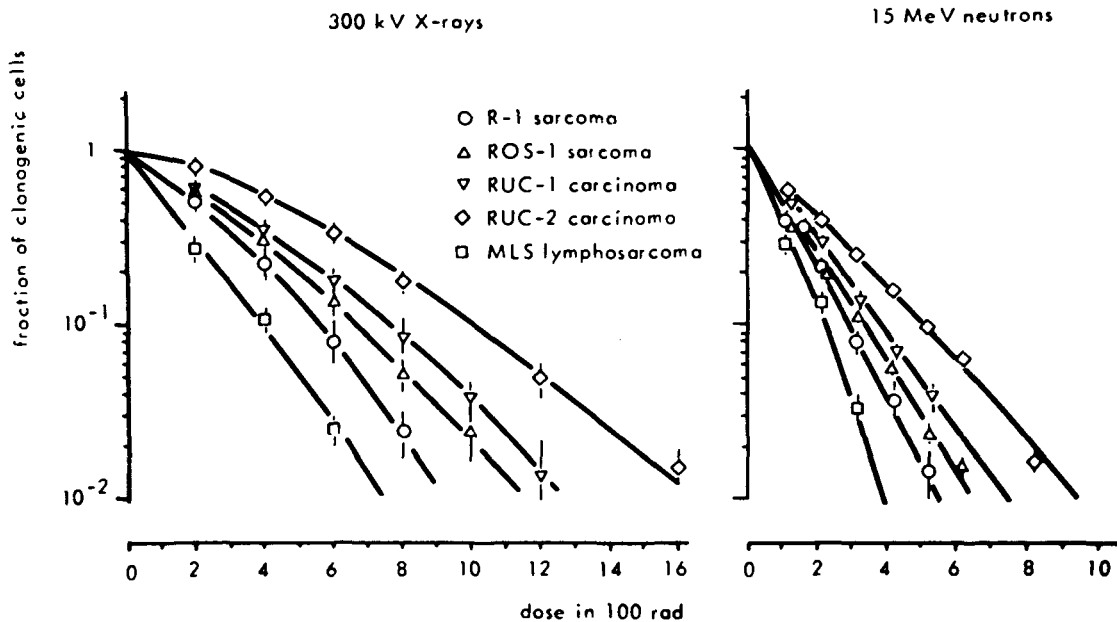


Figure 2

Survival curves of 5 cell lines, in culture, derived from different types of animal tumours after irradiation with 300 kV X-rays or 15 MeV neutrons. The large differences in cell radiosensitivity observed after X-ray irradiation are reduced after neutron irradiation (but not eliminated).

(From Barendsen and Broerse [2])

comparing the responses of 6 cell lines to X-rays and neutrons, observed a modification in their relative radiosensitivities (i.e. a given cell line more resistant to X-rays could be more sensitive to neutrons another cell line) (Fig. 3).

- a reduction in the differences in radiosensitivity related to the position of the cell in the mitotic cycle (Fig. 4) [12].
- less repair phenomena (in general), and as a consequence less difference between the responses of the cell populations to fractionated irradiation (Fig. 5).

From the above arguments, it can be concluded that all cell populations, in all conditions, tend to respond in a more similar way when exposed to neutrons compared to photons. From that point of view, a reduction in OER can be considered as a particular aspect of a more general phenomenon, i.e. a reduced difference in radiosensitivity between cell populations [31] [34].

A reduction in OER is always an advantage, since the normal tissues are - in general - well oxygenated. However, the benefit is often difficult to quantify and it is also difficult to identify those tumours for which the hypoxic cells constitute a major factor of radioresistance (although some information could be derived from the hyperbaric oxygen trials, and from the studies with specific sensitizers of hypoxic cells). A reduction in the differences of intrinsic radiosensitivity, or a reduction in the differences of radiosensitivity related to cell position in the mitotic cycle, or a general

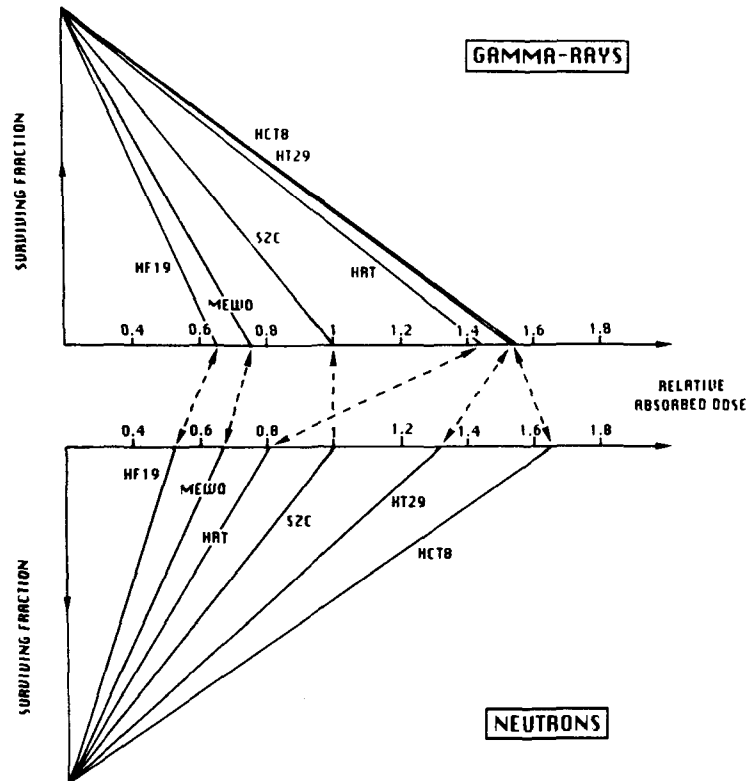


Figure 3

Comparison of survivals for 6 cell lines irradiated with Co-60 gamma rays and d(50)+Be neutrons. Exponential survival curves has been assumed after a fractionated irradiation : $_{\text{eff}}D_0$ were calculated for 2 Gy (γ equiv.) per fraction using the α and β coefficients of the cell survival curves. Relative absorbed doses are indicated : the SZC cell survival curves being taken as a reference (1.00). The variations of radiosensitivity are as important with neutrons than with photons, but the orders are altered. (calculated from the data of Fertil et al. [15]), .

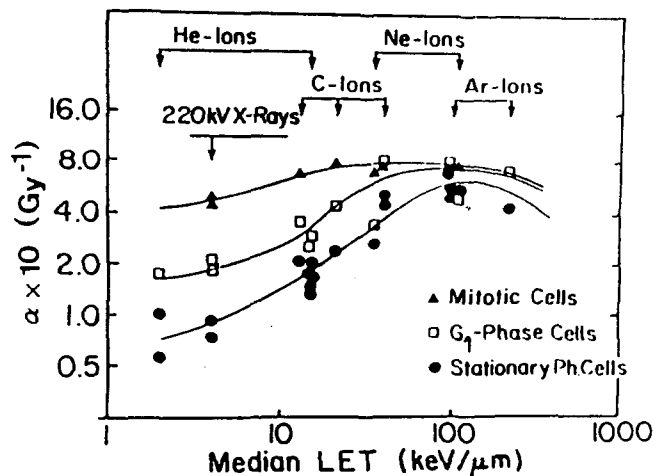


Figure 4

Single-hit inactivation coefficients (α) for homogeneous populations of mitotic, G1-phase, and stationary phase Chinese hamster cells irradiated with 220 kV X-rays and various charged-particle beams, as a function of median LET (in $\text{keV}/\mu\text{m}$).

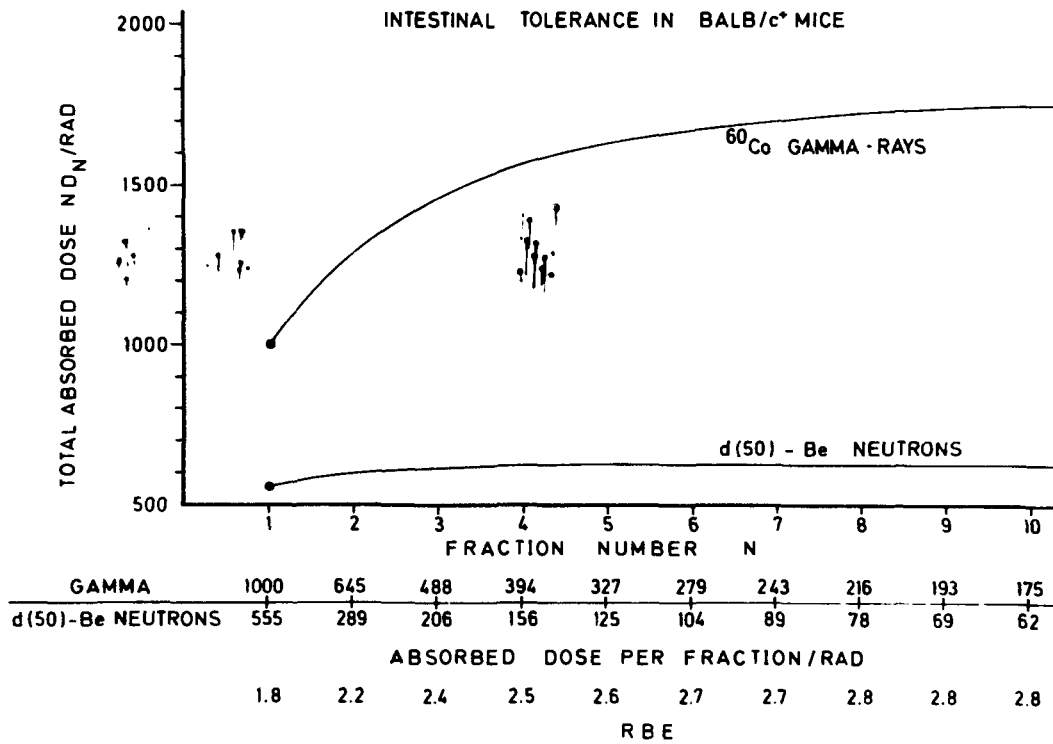


Figure 5:

Isoeffect total dose for early intestinal tolerance in mice. The total dose corresponding to LD₅₀, after fractionated selective abdominal irradiation, is plotted versus the number of fractions and the doses per fraction, for ⁶⁰Co gamma-rays and d(50)+Be fast neutrons. With neutrons the total dose corresponding to LD₅₀ is nearly independent on fraction size. The modification of the shape of the isoeffect dose reflects a reduction of the importance of the repair processes after neutron compared to gamma irradiation.

From Wambersie et al. [34].

reduction in the repair phenomena could bring an advantage or a disadvantage depending on the characteristics of the tumour cell population and of the normal tissue(s) at risk for a particular patient. This raises the important problem of patient selection [34].

When the cancer cell population is more sensitive to X-rays than the normal cell population at risk, there is no benefit at all for using neutrons. On the contrary, neutrons will reduce the difference in radiosensitivity which selectively protects the normal cell population. In the reverse situation, when the cancer cell population is more resistant to X-rays than the normal cell population, neutrons could bring a benefit by reducing a difference in radiosensitivity which selectively protects the cancer cells (or even by killing more selectively some cancer cell lines) (Fig. 6).

Two practical consequences can be derived from the above radiobiological considerations :

1. The importance of patient selection. An absence of (or a wrong) selection of the patients could worsen the clinical results and lead to erroneous conclusions about the

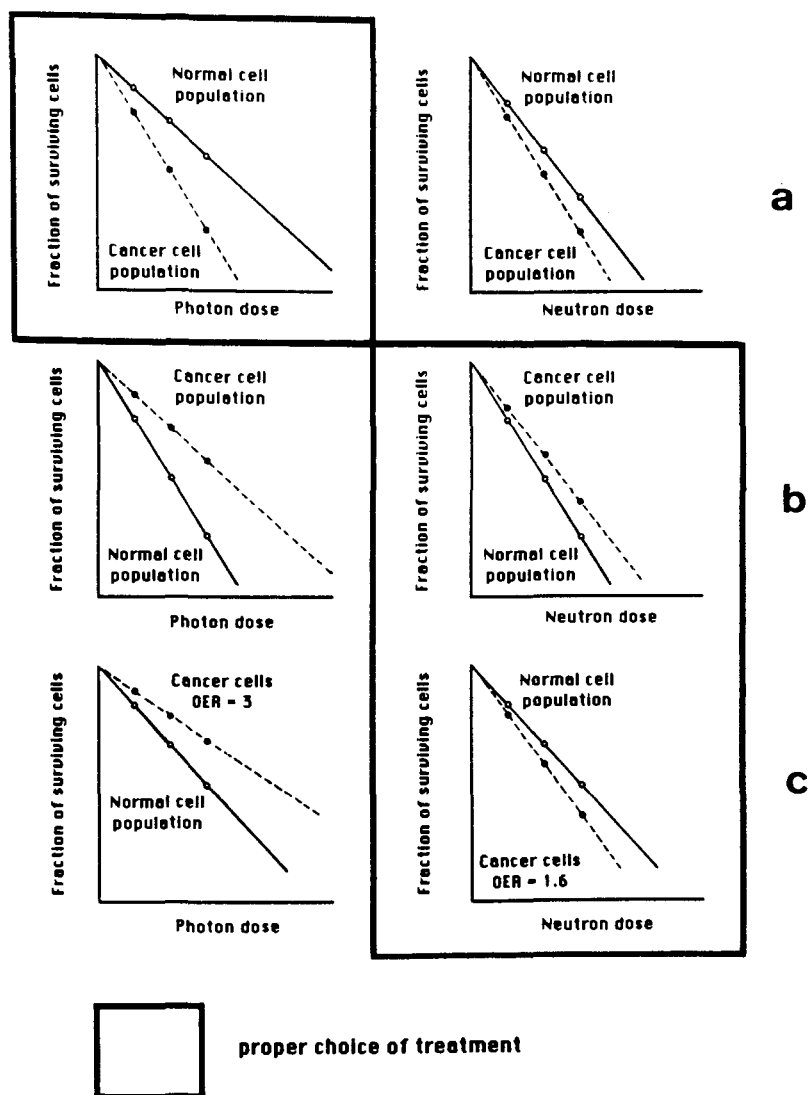


Figure 6

Importance of patient selection for fast neutron therapy.

Three possible clinical situations are considered. In the first one (Fig. 6 a), the cancer cells are more radiosensitive to X-rays than the critical normal cells, and there is no argument at all in using neutrons which would reduce a favourable differential effect. Some typical examples are : seminomas, lymphomas, Hodgkin. As discussed in the text, the differences in radiosensitivity between cell lines are reduced when neutrons are used. It has been assumed that the survival curves after fractionated irradiation are exponential : i.e. a constant proportion of the cells is killed at each sitting. However, the exact shape of the cell survival curve is not essential for the present discussion.

In the second situation (Fig. 6 b), neutrons bring a benefit by reducing a difference in radiosensitivity which selectively would protect the cancer cell population. A third, more favourable, situation can be considered where the relative radiosensitivities are reversed. This could be the case when the greater radioresistance of the cancer cell population to X-rays is due to the presence of hypoxic cells. This possibility is also suggested by the data of Fertil et al. [15].

TABLE II

IMPORTANCE OF PATIENT SELECTION FOR NEUTRON THERAPY			
Assumptions :			
- for 70 % of the patients, photons are the right choice - for 30 % of the patients, neutrons are the right choice - the cure rate is : 60 % if the right treatment is applied 40 % if a wrong treatment is applied.			
Number of patients	cure rate		
	photontherapy to all patients	neutrontherapy to all patients	the right treatment
70	42	28	42 (photontherapy)
30	12	18	18 (neutrontherapy)
100	54	46	60

value of fast neutrons. This could maybe explain a least some of the reported discrepancies in clinical results (Table II).

2. The need for a high physical selectivity with high-LET radiations, which proceeds from the reduced differences in radiosensitivity. When large differences in radiosensitivity are observed between the cancer and normal cell populations, a poor physical selectivity is of limited consequence. In typical cases, such as seminomas or lymphomas, the dose prescribed to the target volume is below the tolerance dose, and irradiation of a few additional cm³ of normal tissue would be of little clinical importance (in chemotherapy, there is obviously no physical selectivity at all, and the potential therapeutic gain depends only on a biological selectivity). By contrast, when the differences in radiosensitivity are reduced with very high-LET radiation, the therapeutic efficiency mainly rests on a high level of physical selectivity; sparing a few cm³ of normal tissues then becomes of real importance.

In addition, with low-LET radiations, where repair phenomena play an important role, differences in repair capacity between the normal and cancer cell populations

can be exploited by selecting appropriate fractionation regimen. This possibility is reduced with high-LET radiations since repair phenomena are in general smaller. Consequently, from a radiobiological point of view, high-LET radiations then appear to be a treatment modality with limited possibility of enhancing an eventual differential effect by selecting the optimum fraction sizes.

2. Clinical data - Survey of fast neutron therapy

The clinical data at present available for high-LET radiations were to a large extent obtained with fast neutrons. As a matter of fact, only limited patient series were treated at Berkeley with heavy ions : they will be considered in section C. We shall not review here the results of pi-meson therapy, since pi-mesons cannot be considered as pure high-LET radiations.

Fast neutron therapy is applied routinely in about twenty centres throughout the world (Table III). Over 10 000 patients have been treated so far with neutrons, either as the sole irradiation modality or in combination with other radiotherapy techniques, the longest follow-up exceeding 15 years. The available clinical data now enable us to identify the tumour types and/or sites for which neutrons were shown to bring a benefit, and, on the other hand, tumours for which neutrons should not be used. In addition, there are tumour sites for which the available information is incomplete or for which the reported results are conflicting [28] [33].

The tumours for which fast neutrons were found to be superior to conventional X-rays are listed in Table IV. They are, in general, slowly growing and well differentiated : salivary gland tumours (Table V) [17] [20] [30], paranasal sinuses (Table VI) [14], some locally advanced tumours of the head and neck with fixed metastatic lymph nodes [18] [19], soft tissue sarcomas (Table VII) [23], bone- and chondrosarcomas [23], prostatic adenocarcinomas (Fig. 7) [27], melanomas [36]. By contrast, disappointing results were obtained for brain tumours [28]; these observations are in agreement with the radiobiological data and especially the high RBE value observed for CNS. However, a possible benefit for neutron boost in brain tumours should be further investigated [9]. In addition, neutrons should not be used for tumours showing an exquisite radiosensitivity to X-rays (e.g. seminomas, lymphomas, or in general poorly differentiated, rapidly growing tumours), and for which neutrons would then reduce a favourable differential effect.

A third group of tumours includes those tumour types for which further studies are necessary. However, when evaluating the results, at least 2 factors need to be taken into account :

- a) some of the conflicting results which were reported could be related to differences in patient recruitment, and to the fact that in some studies it was not possible to identify the patient "subgroups" for which neutrons could bring a benefit. In that respect, the development of individual predictive tests is essential.
- b) in many centres, and especially in the first patient series, neutron treatments were applied in "sub-optimal" technical conditions (e.g.: beam penetration, skin sparing,

TABLE III

THE NEUTRON THERAPY FACILITIES IN THE WORLD		
Centre	Neutron Producing Reaction	Comments
EUROPE		
MRC-Clatterbridge, U.K.	p(62)+Be	rotational gantry variable collimator
Orléans, France	p(34)+Be	vertical beam
UCL- Louvain-la-Neuve, Belgium	p(65)+Be	vertical beam (multileaf collimator and horizontal beam in preparation)
Hamburg, Fed.Rep.Germany	(d + T)	rotational gantry
Heidelberg, Fed.Rep.Germany	(d + T)	"
Munster, Fed.Rep.Germany	(d + T)	"
Essen, Fed.Rep.Germany	d(14)+Be	rotational gantry
UNITED STATES		
M D Anderson- Houston, Texas	p(42)+Be	rotational gantry variable collimator
Cleveland, Ohio	p(43)+Be	horizontal beam
UCLA - Los Angeles	p(46)+Be	rotational gantry variable collimator
Seattle, Washington	p(50)+Be	rotational gantry multileaf collimator
Fermilab	p(66)+Be	horizontal beam
ASIA		
National Institute of Radiological Sciences (NIRS) - Chiba, Japan	d(30)+Be	vertical beam multileaf collimator
Institute for Medical Sciences (IMS) - Tokyo, Japan	d(14)+Be	horizontal beam
Korea Cancer Center Hospital (KCCH) - Seoul, Korea	d(50.5)+Be	rotational gantry
King Faisal Hospital - Riyadh, Saudi Arabia	p(26)+Be	rotational gantry
AFRICA		
National Accelerator Centre (NAC) Faure, Rep.South Africa	p(66)+Be	rotational gantry variable collimator

From ICRU [22] and Tsunemoto et al. [30]

TABLE IV

CLINICAL INDICATIONS FOR NEUTRON THERAPY (SUMMARY)	
1.	SALIVARY GLAND TUMOURS locally extended, 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
6.	MELANOMAS inoperable/recurrent.

From Wambersie et al., [36]

fixed beams, etc...). These technical factors could bias the conclusions that one would derive concerning the value of fast neutrons. For example, one cannot derive valid conclusions from bladder tumours irradiated with d(16)+Be beams [13]. Similarly, the difficulty of treating cervix tumours with a fixed horizontal beam was stressed at TAMVEC [25].

As far as the proportion of patients, suitable for neutron therapy is concerned, figures ranging from 10 to 20 % have been suggested; they correspond to the percentages of radiotherapy patients for which neutrons were shown to be superior than conventional X-rays. These percentages are probably at the lower limit of the indications of high-LET radiations, since they were often obtained with poor physical selectivity (e.g. low-energy cyclotrons). It is likely that with high-energy, hospital-based modern cyclotrons, and especially heavy ions, high-LET will be found to be useful for a larger proportion of patients.

C. The rationale for heavy ion therapy

Heavy ions combine the advantage of a high physical selectivity with the potential advantage of high-LET radiation for the treatment of some tumour types. As far as the physical selectivity is concerned, heavy ion beams are similar to proton or helium ion beams; they have even a smaller penumbra but it is questionable whether this factor could be of clinical relevance. More important is the fact that, with heavy ions, the

TABLE V

REVIEW OF THE LOCO-REGIONAL CONTROL RATES FOR MALIGNANT SALIVARY GLAND TUMOURS TREATED DEFINITELY WITH RADIATION THERAPY			
FAST NEUTRONS			
Authors	Number of patients *	Loco-regional control (%)	
Saroja et al., 1987	113	71	(63 %)
Catterall and Errington, 1987	65	50	(77 %)
Battermann and Mijnheer, 1986	32	21	(66 %)
Griffin et al., 1988	32	26	(81 %)
Duncan et al., 1987	22	12	(55 %)
Tsunemoto et al. (in press)	21	13	(62 %)
Maor et al., 1981	9	6	
Ornitz et al., 1979	8	3	
Eichhorn, 1981	5	3	
Skolyszewski, 1982	3	2	
Overall	310	207	(67 %)
LOW-LET RADIOTHERAPY PHOTON AND/OR ELECTRON BEAMS, AND/OR RADIOACTIVE IMPLANTS			
Authors	Number of patients *	Loco-regional control (%)	
Fitzpatrick and Theriault, 1986	50	6	(12 %)
Vikramet et al., 1984	49	2	(4 %)
Borthne et al., 1986	35	8	(23 %)
Rafla, 1977	25	9	(36 %)
Fu et al., 1977	19	6	(32 %)
Stewart et al., 1968	19	9	(47 %)
Dobrowsky et al., 1986	17	7	(41 %)
Shidnia et al., 1980	16	6	(38 %)
Elkon et al., 1978	13	2	(15 %)
Rossmann, 1975	11	6	(54 %)
Overall	254	61	(24 %)

* Patients treated de novo and for gross disease after a post-surgical recurrence are included, but not patients who were treated postoperatively for microscopic residual disease.

Updated from B.R.Griffin et al. [17] , T.W. Griffin et al. [20], and Tsunemoto et al. [30]

TABLE VI

RESULTS OF TREATMENT WITH 7.5 MeV NEUTRONS FOR ADVANCED TUMOURS OF PARANASAL SINUSES : HISTOLOGICAL TYPES, RESPONSES AND COMPLICATIONS			
Histological type	Regressing completely n (%)	Recurring n (%)	With complications n (%)
Squamous (n = 17)	14	3	3
Adenoid cystic (n = 11)	10	4	4
Adenocarcinoma (n = 8)	6	-	1
Transitional cell (n = 5)	5	1	2
Undifferentiated (n = 1)	1	-	-
Malignant melanoma (n = 1)	1	-	-
Total (n = 43)	37 (86)	8 (18)	* 10 (23)

* 2 of these from 8 patients who had received previous photon radiotherapy

From Errington [14]

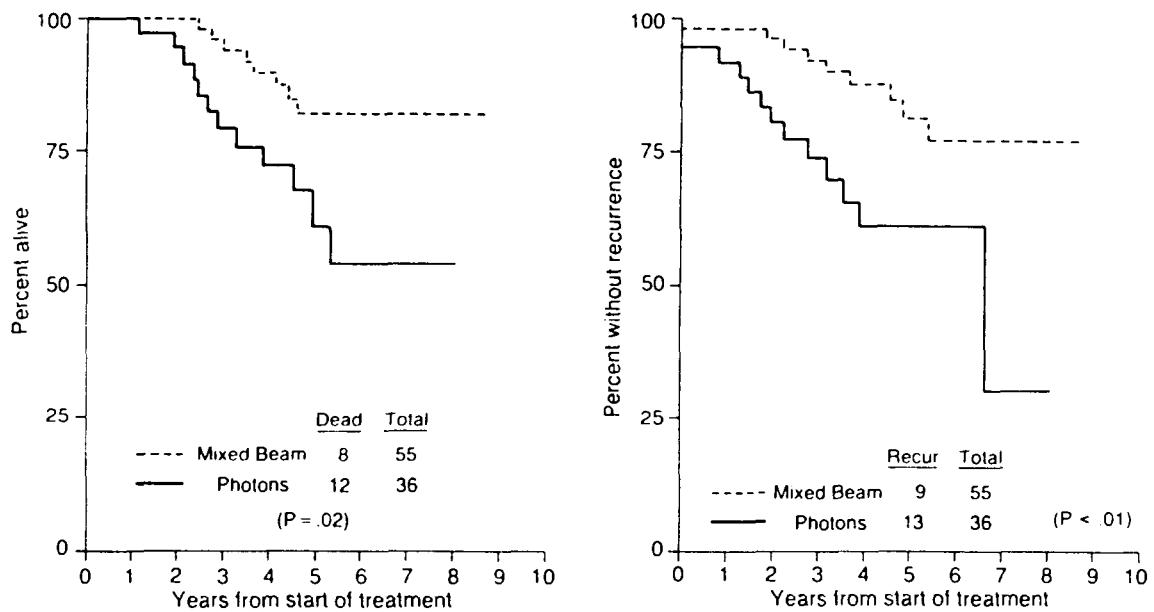


Figure 7

RTOG randomized trial comparing a combination of fast neutrons and photons ("mixed-beam") and conventional photon irradiation alone.

At the left hand side, the actuarial survivals at 8 years are indicated, adjusted by exclusion of intercurrent noncancer death ("determinantal" survival rates).

At the right hand side, the local control rates are indicated, combining clinical and biopsy criteria.

From Russell et al.[27].

TABLE VII

REVIEW OF THE LOCAL CONTROL RATES FOR SOFT-TISSUE SARCOMAS TREATED DEFINITELY WITH RADIATION THERAPY			
NEUTRONS			
Institutions	Number of patients *	Local control (%)	
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			
Institutions	Number of patients *	Local control (%)	
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	(33 %)
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., [23]

higher RBE at the level of the spread-out Bragg peak further improves the advantage of the dose distribution. Furthermore, the high-LET at the level of the spread-out bragg peak alters the biological effect and this has to be taken into account when prescribing the irradiation modality (e.g. fractionation). The LET depends on the type of particles as well as on the width of the spread-out Bragg peak; factors such as RBE, OER, and repair capacity should then be determined.

The energies required to obtain a sufficient beam penetration are typically :

- for carbon ions : 400 MeV/amu;
- for neon ions : 620 MeV/amu
- for argon ions : 860 MeV/amu

Heavy ion therapy programs are justified by three sets of arguments :

- 1) the radiobiological and clinical data indicating that, for the treatment of some tumours types and/or sites, high-LET radiations could bring a benefit compared to low-LET radiations.

Radiobiology indicates that high-LET radiations could be of interest for the treatment of some tumour types, and further suggests some mechanisms through which they can bring a benefit (see Section B.1).

Review of the clinical results of fast neutron therapy indicates that indeed neutrons can bring a benefit for several tumour types or sites (see Section B.2).

- 2) the importance of a high physical selectivity which has been clearly demonstrated with low-LET radiations. The benefit of replacing 200 kV X-rays by high energy photons has been proven, as well as the benefit of further improving the physical selectivity - for some selected tumour sites - by the introduction of proton beams (see Section A.)

The available radiobiological data indicate that a high physical selectivity is even more important with high- than with low-LET radiations due to a general reduction in the difference of radiosensitivity between cell populations (see Section B.1).

- 3) the encouraging clinical results reported from Berkeley are an additional argument, although they were obtained on limited, selected groups of patients (Table VIII).

The best results obtained at Berkeley with neon ions were obtained for those tumours for which fast neutrons were shown to be of interest. The results obtained at Berkeley with helium ions are also presented on Table VIII. Comparison between helium and neon ions is difficult since the patient series are too small and not comparable. In particular, the soft tissue sarcomas treated with neon ions were far most advanced, and the clinical impression clearly suggests a greater efficiency of neon ions (which is not reflected in the results presented in Table VIII).

TABLE VIII

SUMMARY OF THE CLINICAL RESULTS OBTAINED WITH HELIUM IONS AND NEON IONS AT BERKELEY			
Tumour site	Local control rate with :		
	Helium ions	Neon ions	Conventional Treatment
Salivary gland		80 % (10 patients)	28 % (188 patients) (Literature review)
Nasopharynx Paranasal sinus	53 % (13 patients)	63 % (21 patients)	21 % (97 patients) (UCSF)
Sarcoma	65 % (17 patients)	45 % (24 patients)	28 % (Literature review)
Prostate	(Literature review)	100 %	60-70 % (9 patients)
Lung	(UCSF)	39 %	22-40 % (18 patients)
Glioblastoma Brain		Median survival: 17 months (13 patients)	Median survival: 9-12 months (UCSF, RTOG, NCOG)

Modified from J.R. Castro, [10].

The general principles of patient selection for heavy-ion beam therapy are presented on **Table IX**. Two main groups of indications can be identified depending whether the biological effects of high-LET radiations (A) or the high physical selectivity of the beams (B) is thought to be the most important factor. In addition, more specific indications can be proposed (C).

Concerning the first group of indications (for which the high-LET is considered to be most important), it is possible to make a tentative prediction of the clinical benefit which could be expected from heavy ion beams by considering both the conclusions of the neutron studies and the heavy ion results from Berkeley. **Table X** summarizes and compares both series of clinical results.

TABLE IX

GENERAL PRINCIPLES OF PATIENT SELECTION FOR HEAVY-ION BEAM THERAPY	
To take advantage of the biological AND physical characteristics of the beams	
A	- The radiobiological advantage (high-LET) is thought to be the most important factor, followed by the physical selectivity of the beams
	a. where high-LET radiation already demonstrated to be useful <ul style="list-style-type: none"> - salivary gland tumours - paranasal sinuses - fixed lymph nodes - prostatic adenocarcinomas - sarcomas, etc.
	b. where additional information is needed <ul style="list-style-type: none"> - pelvic tumours : bladder, rectum, cervix, etc. - other tumours : stomach, biliary duct, etc.
B	- The physical selectivity (dose distribution) of the beams is thought to be the most important factor followed by the radiobiological advantage of high-LET
	Tumours in technically difficult situations, but where high-LET radiation may be better than low-LET radiation (e.g. slowly growing tumours) <ul style="list-style-type: none"> - <u>adjacent to CNS</u> : meningioma, pharyngioma, chordoma, optic nerve, glioma, AVM, paraspinal cord tumour, paraaortic lymph node, etc. - <u>root of neck disease</u> : upper oesophagus, post cricoïd carcinoma, etc - <u>thoracic disease</u> : tumour of the lung with mediastinal disease after resection of primary, mesothelioma, etc.
C	- Additional indications <ul style="list-style-type: none"> - where possible later surgery should not be prejudiced : tongue, avoiding mandible, etc. - tumours in children - very poor prognosis disease : unresectable hepatoma, pancreas, retroperitoneal sarcoma, recurrent after previous radiotherapy, etc. .

After G.R.H. Sealy in [38].

Two types of comments need to be made here. Firstly, the patient series are not fully comparable (they were not randomized) and one should then be careful before deriving definite conclusions from their comparison. Secondly, **Table X** probably reflects a lower limit of what could be expected with heavy ions, since -as often stressed- neutrons were, in many centres, not applied in optimal technical conditions. A similar remark also applies, but for other reasons, to the neon results for which in addition there was a severe patient selection.

TABLE X

SUMMARY OF THE CLINICAL RESULTS OBTAINED WITH HIGH-LET RADIATIONS (FAST NEUTRONS AND NEON IONS)		
Tumour site (or type)	Local control rates after :	
	<u>Fast neutrons</u>	<u>Neon ions</u>
- salivary gland tumours	67 % (24 %)	80 % (28 %)
- paranasal sinuses	67 %	63 % (21 %)
- fixed lymph nodes	69 % (55 %)	
- sarcomas	53 % (38 %)	45 % (28 %)
- prostatic adenocarcinomas	77 % (31 %)	100% (60-70 %)

() for comparison, the local control rates currently obtained with conventional low-LET radiations (see Tables V, VI, VII, VIII, and Fig. 6)

Concerning the second group of indications for heavy ions (for which the physical selectivity is considered to be the most important factor), we can normally expect the same results as with protons, but with the additional advantage of high-LET radiations for slowly growing tumours. Heavy ions could extend the field of the indications of radiation therapy by allowing the oncologists to envisage irradiation of groups of tumours "traditionally" considered to be radioresistant (e.g. adenocarcinomas).

Only a few heavy-ion therapy facilities are planned in the world : the facility at the NIRS in Japan which is under construction, the LIBRA project in the USA, and in Europe the GSI project in Darmstadt-FRG and the EULIMA project. Due to their high cost and complexity, an international cooperation is necessary in order to ensure a rapid exchange of information and an appropriate patient recruitment. Patient recruitment should in principle aim at :

- selecting for heavy ions tumour types or sites for which there is evidence that better results could normally be expected than with conventional treatments (see e.g. **Table IX A**);
- initiating randomized trials designed to answer specific questions of great relevance in radiobiology and/or radiation therapy.

In photon therapy, an accuracy on dose delivery as high as 3.5 % (i.e. one standard deviation on the absorbed dose at the specification point) is required. This requirement is due to the steepness of the dose-effect relations for local tumour control

and normal tissue complications. For high-LET radiations, the available clinical and radiobiological data indicate that the dose-effect relations are as steep as those observed for photons, and consequently the same degree of accuracy has to be achieved. Furthermore, as discussed above, at least the same physical selectivity (dose distribution) is required due to a reduced differential effect with high-LET radiations.

Further research on nuclear and molecular data is then justified for the different components of human (and biological) tissues and detectors, as well as for materials used for the beam collimation and shielding. Acquisition of data should be extended to the types of particles and energy ranges considered in this report.

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First Research Co-ordination Meeting on
ATOMIC AND MOLECULAR FOR RADIOTHERAPY

IAEA Headquarters, Vienna
30 January - 2 February 1989

AGENDA

Monday, 30 January, 9:30 hrs

Opening, Selection of Chairmen (M. Inokuti and L.H. Toburen),
Adoption of Agenda
Short remarks by the Scientific Secretary on this CRP

SESSION I-1 Presentation of Current Activities

A. Wambersie: The future of high-LET radiation in cancer
therapy - Justification of heavy-ion therapy programme

SESSION II-1 Brief Reports by CRP Participants

- activities completed/being done
- special problems encountered
- plans for the future
- additional tasks to be considered

T. Märk
L.H. Toburen

SESSION I-2 Presentation of Current Activities (cont.)

D.T. Goodhead: Analysis of the role of radiation quality
in determining biological effectiveness

SESSION II-2 Brief Reports by CRP Participants (cont.)

M. Terrissol
L. Sanche
Y. Hatano

Tuesday, 31 January, 09:00 hrs

SESSION I-3 Presentation of Current Activities (cont.)

M.J. Berger: Stopping powers of p and α particles

SESSION II-3 Brief Reports by CRP Participants (cont.)

M. Inokuti
Z. Herman
H. Paul
M.J. Berger

SESSION I-4 Presentation of Current Activities (cont.)

L. Sanche: Interactions of low energy electrons with molecular solids

SESSION II-4 Brief Reports by CRP Participants (cont.)

D. Srdoc

D.T. Goodhead

Wednesday, 1 February, 09:00 hrs

SESSION I-5 Presentation of Current Activities (cont.)

M. Inokuti: Subexcitation electrons

SESSION III Discussions on Final Publication, Time schedule

SESSION IV Working Group Discussions,

SESSION V Reports by Working Groups Leaders

Thursday, 2 February, 09:00 hrs

SESSION VI Plenary session to discuss the Conclusions & Recommendations

First Research Co-ordination Meeting
on ATOMIC and MOLECULAR DATA FOR RADIOTHERAPY

IAEA Headquarters, Vienna
30 January - 2 February 1989

LIST OF CRP PARTICIPANTS

Name	Title of Project
1. Tilman MAERK (5274/CF) University of Innsbruck Austria	"Partial and total ionization cross sections for atoms, molecules and clusters"
2. Léon SANCHE (5275/CF) University of Sherbrooke Canada	"Mechanism of low-energy electron interaction with the organic and biologic substances in the condensed phase"
3. Yoshiko HATANO (5276/CF) Tokyo Inst. of Technology Japan	"Cross sections for the interaction of photons with molecules"
4. Larry TOBUREN (5277/CF) Pacific Northwest Laboratory U.S.A.	"Study of cross sections for electron production in heavy ion collisions with atomic and molecular target"
5. Martin J. BERGER (5278/CF) National Inst. of Standards and Technology U.S.A.	"Cross sections for the interaction of photons and charged particles with atoms and molecules"
6. Helmut PAUL (5287/CF) University of Linz Austria	"Influence of physical state and chemical bond on proton stopping"
7. Michel TERRISSOL (5288/CF) University of Paul Sebatier France	"Simulation of chemical species evolution following irradiation"
8. Herwig G. PARETZKE (5289/CF)* GSF Inst. for Radiation Protection Fed. Rep. of Germany	"Calculation of track structure quantities needed for radiation therapy"
9. Dudley GOODHEAD (5290/CF) Medical Research Council United Kingdom	"Energy desposition by radiation tracks in target structures of dimensions in the range 1-100 nanometres"
10. Mitio INOKUTI (5291/CF) Argonne National Laboratory U.S.A.	"Electron degradation spectra and yields of ions and excited states"

* CSI did not attend the meeting

- | | |
|--|---|
| 11. Ilja KAPLAN (5292/RB)*
Karpov Inst. of Physical
Chemistry
U.S.S.R. | "Development of physico-chemical model
and producing code for calculation of
track structures and W-values of
electrons and protons in tissue-
equivalent media and their phase-
dependence" |
| 12. Dusan SRDOC (5293/RB;
CSI: B. Obelic)
Ruder Boskovic Institute
Yugoslavia | "The ionization yield for low energy
photons and electrons absorbed in poly-
atomic gases and tissue-equivalent gas
mixtures" |
| 13. Zdenek HERMAN (5398/RB)
J. Heyrovsky Inst. of
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Czechoslovakia | "Data on processes of rapid conversion
of initial ions and excited neutral
through collisions with other
molecules" |

* CSI did not attend the meeting

First Research Co-ordination Meeting
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IAEA Headquarters, Vienna
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Coordinated Research Programme on
ATOMIC AND MOLECULAR DATA FOR RADIOTHERAPY

Institute Chief Sci. Investigator Research Agreement No. or Research Contract No.	Proposed Programme	Report at First RCM
University of Innsbruck (Austria) Tilman Märk 5274/CF	<ol style="list-style-type: none"> 1) Experimental determination of partial and total electron impact ionization cross sections of selected atoms and molecules. 2) Theoretical studies on electron impact ionization cross sections (partial and total). Calculations and development of new formulae for atoms and molecules. 3) Electron-cluster interaction. Ionization mechanism and ionization efficiency as a function of cluster size. 	<ul style="list-style-type: none"> - Development of new experimental method to measure partial ionization cross sections for fragment ions. Evaluation of the accuracy of method. - Presentation of a new semi-classical formula for the calculation of single ionization of ground state atoms and excited state atoms. - Contribution of autoionization effects for elements of the middle rows of the periodic table. - Additivity rule and its failure in case of molecular radicals. - Vibrational energy transfer in N₂ and O₂ cluster ions. - Electron impact ionization production of multiply charged cluster ions. Coulomb explosion. - Electron attachment to O₂ clusters.
Tokyo Inst. of Technology (Japan) Yoshio Hatano 5276/CF	Measurement, compilation and evaluation of: <ol style="list-style-type: none"> 1) Cross-sections for photo-absorption, -ionization, and -dissociation of molecules in the VUV-SX region. 2) Cross sections for electron interactions with molecules in dense media. 3) Cross sections for the reactions of excited molecules. 	<ul style="list-style-type: none"> - Cross sections for photo-absorption, -ionization, and -dissociation of molecules in the VUV-SX region. - Electron attachment and recombination in dense media. - Cross sections for the de-excitation of He(2¹p) by atoms and molecules and their collisional energy dependence.

Institute Chief Sci. Investigator Research Agreement No. or Research Contract No.	Proposed Programme	Report at First RCM
University of Sherbrooke (Canada) Léon Sanche 5275/CF	<p>Proposed programme on low-energy interaction with <u>condensed molecules</u> will:</p> <ol style="list-style-type: none"> 1) provide low-energy electron scattering cross sections for elastic, vibrational, librational and electronic excitation and dissociative attachment and ionization of condensed atoms and molecules. 2) describe the mechanism involved in the scattering processes from experimental data. <p>The above data will be obtained for condensed rare gases and condensed molecules of biological interest including H₂O, O₂, N₂, CO₂, CO and various hydrocarbons. <u>Absolute</u> cross section values will be obtained for H₂O and O₂.</p>	<ul style="list-style-type: none"> - Ultrafast reactions of slow electrons in condensed matter. - Brief outline of programme, see left column. <p><u>Lecture</u> "Electron phase of condensed materials", Ref. <u>Interaction of slow electrons with atoms and molecules in solid films</u>, Léon Sanche, Radiat.Phys. Chem. <u>32</u>(1988)269; Int.J. Radiat.Appl.Instrum., Part C.</p>
Pacific Northwest Laboratory (USA) Larry H. Toburen 5277/CF	<ol style="list-style-type: none"> 1) Review of total and differential ionization cross sections for ions of H, He, C, O and N. 2) Extensions of measurements of differential ionization cross sections for C and O ions in atomic and molecular gases. 3) Investigation of screening by projectile electrons on differential ionization cross sections for ions with mass <20 amu and energy E ≤ 1MeV/amu. 4) Investigation of cross section scaling for low energy (E ≤ 1MeV/amu) ions with mass ≤ 20 amu in atomic and molecular targets. 	<ul style="list-style-type: none"> - Interpretation of systematics of electron emission, double differential cross-sections for intermediate velocity ions. - Presentation of data for carbon and oxygen ions with energies of a few tenths of an MeV/amu for effects of electronic screening on electron production cross sections in order to seek charge scaling relationship. (O⁺ on Water vapor, C⁺ on Ne and others)

Institute
Chief Sci. Investigator
Research Agreement No.
or Research Contract No.

Proposed Programme

Report at First RCM

National Inst. of Standards
and Technology
(USA)
Martin J. Berger
5278/CF

To review experimental and
theoretical information
on charged-particle
stopping powers and ranges:
1) for electrons, from
10 keV to 10 GeV;
2) for protons, from 1 keV
to 10 GeV;
3) for alpha particles,
from 10 keV to 1 GeV.
To the extent possible,
provide computerized
stopping-power data
bases.

Introduction of works on
- Photons;
. data base of cross section
attenuation coefficients
. energy absorption
coefficients
. bibliography of cross
sections for compounds.
- Electrons;
. differential cross
sections for elastic scat-
tering by atoms
1 keV to 1 MeV
for Z=1 to 100
some results from posi-
trons
. electron density distribu-
tion; screened Coulomb
potential
partial wave expansion
- 3 Dimensional dose distri-
bution from electron beam;
. H₂, low Z plastics: 0.5
to 50 MeV
. pencil beams

Lecture

"Stopping powers of p and α
particles", Ref. ICRU
report (in preparation)

[Note]

This ICRU report, when ready
(even as draft), is request-
ed to be sent to H. Paul
and Scientific Secretary.
[Request to Sci. Secretary]
The necessary procedure to
invite Hans Bichsel to the
next CRP meeting.

University of Paul Sabatier
(France)
Michel Terrissol
5288/CF

1) Calculation of yields and
G values as a function of
dose rate using a time
space dependent Monte-
Carlo code simulating
evolution of chemical
species.
2) Intercomparison of
various codes used
for track structure
calculation.

Electron and photon cross
sections in the low energy
region were described.
Also calculation of particle
transport using Monte Carlo
technique was discussed.
Yields of species, e_{aq}, H_{aq},
H₂O etc were presented as a
function of times following
energy deposition by radiation
in pure water.

Institute Chief Sci. Investigator Research Agreement No. or Research Contract No.	Proposed Programme	Report at First RCM
University of Linz (Austria) Helmut Paul 5287/CF	1) Influence of physical state and chemical bond on proton stopping power, a. comparison in various types of carbon b. measurement for solid H ₂ O. 2) Evaluation of published stopping power data for protons in selected elements.	- Influence of physical state and chemical bond on proton stopping power (STP). . STP for C,Al,Si,Ni,Cu,Ge, Ag and Au 30 < E _p < 500 keV . STP for Al ₂ O ₃ , SiO ₂ and H ₂ O (vapor) [Note] STP for Mg and Al (for detector) and for different phases of carbon are to be added. [Request to relevant participant] Send to Paul STP compilation by D. Powers and STP data file by J.F. Janni.
GSF Institute for Radiation Protection (FRG) Herwig P. Paretzke 5289/CF	Calculation of track structure quantities for: electrons of energies 10 keV to 10 MeV protons of energies 1 keV to 400 MeV alpha-particles of energies 10 keV to 400 MeV/amu, and Be,B,C,N,O, ions of energies 100 keV/amu to 20 MeV/amu In Water, DNA and several gases.	- Because of his operation CSI could not attend the RCM. [Note] CSI is requested to assume the responsibility for Chapter 9 of the final publication, i.e. Track structure quantities.
Argonne National Laboratory (USA) Mitio Inokuti 5291/CF	1) Yields of ions (w) and other initial products (G) and fluctuations (F). 2) Electron degradation spectra. 3) Cross sections for ions, electrons and photons. In particular, critical assessment of data, analytic fitting of data, systematics of data over different targets.	Brief outline of the programme mentioned in left column. <u>Lecture</u> "Subexcitation electrons", Ref. <u>Subexcitation electrons in gases</u> , M. Inokuti, a chapter of a monograph, "Molecular Processes in Space" to be published by Plenum Press (1989).

Institute Chief Sci. Investigator Research Agreement No. or Research Contract No.	Proposed Programme	Report at First RCM
Medical Research Council (United Kingdom) Dudley T. Goodhead 5290/CF	Extensive consistent tabulated data sets for absolute frequency distributions of energy deposition by electrons, protons, alpha-particles, photons and possibly neutrons in biological macromolecular structures, such as DNA, nucleosomes, and chromatin.	Outline of score frequency distributions of energy deposition <u>in</u> : cylinders of diameter $d = 1 - 500$ nm, and length $l = d/2 - 8d$ <u>for</u> : protons 0.3-5 MeV α -particles 1.2-20 MeV ultrasoft x-rays 0-3 keV upward monoenergetic electrons 0.1 keV upward hard X-rays (selected spectra) selected radionuclides neutrons (possibly) heavier ions (possibly) <u>Lecture</u> "Analysis of the role of radiation quality in determining biological effectiveness", Ref. <u>Track structure analysis of ultra soft X-rays compared to high & low-LET radiation</u> , D.T. Goodhead, H. Nikjoo, Int. J. Radiat. Biol. (in press 1988), <u>Energy deposition in small cylindrical targets by ultrasoft X-rays</u> , H. Nikjoo, D.T. Goodhead, D.E. Charlton, H.G. Paretzke, Phys.Med.Biol. (in press 1988)
Karpov Institute of Physical Chemistry (USSR) Ilja Kaplan 5292/B	1) Study of space distribution of absorbed energy and phase-dependence of W-values for liquid water and water vapour irradiated by electrons. 2) Study of charged particle track structure. 3) Study in detail of absorbed energy distribution for thin layers by electrons and protons. 4) Calculations of radiolysis kinetics in water solutions by electrons and heavy ions.	- Due to other commitment, CSI could not attend RCM. [Note] CSI is requested to join in the writing of Chapter 9 of final publication, i.e. Track structure quantities.

Institute Chief Sci. Investigator Research Agreement No. or Research Contract No.	Proposed Programme	Report at First RCM
Ruder Boskovic Institute (Yugoslavia) Dusan Srdoc (CSI: B. Obelic) 5293/RB	Measurements of: 1) W-values for low-energy photons and electrons in polyatomic gases and tissue-equivalent gas mixtures. 2) Statistical fluctuation in ionization yield for low energy photons absorbed in polyatomic gases and tissue-equivalent gas mixtures.	Report based on the paper by I.K. Bronic, D. Srdoc, and B. Obelic, "The mean energy required to form an ion pair for low-energy photons and electrons in poly-atomic gases", Radiation Research <u>115</u> (1988)213-222.
J. Heyrovsky Institute of Physical Chemistry and Electrochemistry (Czechoslovakia) Zdenek Herman 5398/RB	Evaluation of data on processes of conversion of initial ions and excited neutrals in collisions with other molecules. This includes rate processes of slow ions, cluster ions, and excited neutrals, energetics of species involved.	Processes of conversion of ions and excited neutrals in collision with other molecules, <u>especially with gas phase of water molecules</u> . Outline of evaluation was briefly explained. [Reminder note] Arrangement to avoid overlapping parts with Hatano's work is to be done.
Université Catholique de Louvain (Belgium) André Wambersie Advisor to the CRP	Participation and consultation on the final report of the CRP.	Presentation of the Introduction Chapter (draft) of the final report. <u>Lecture</u> "The future of high-LET radiation in cancer therapy - Justification of heavy-ion therapy programme"