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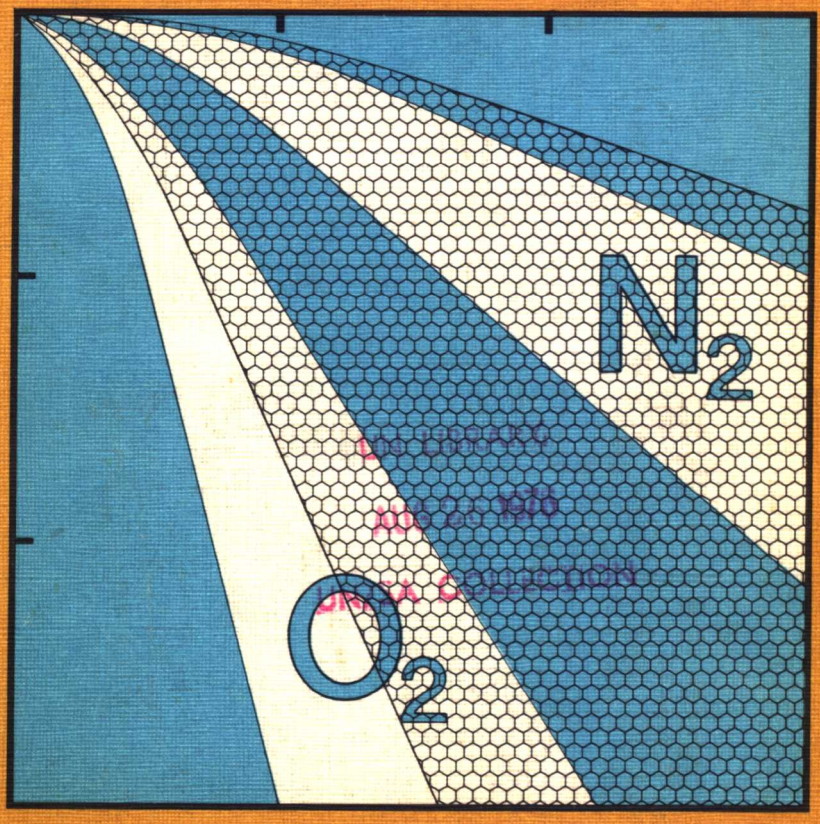
8-11 DECEMBER 1975



MODIFICATION OF RADIOSENSITIVITY OF BIOLOGICAL SYSTEMS

INTERNATIONAL ATOMIC ENERGY AGENCY, VIENNA, 1976

PANEL PROCEEDINGS SERIES

MODIFICATION OF RADIOSENSITIVITY OF BIOLOGICAL SYSTEMS

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MODIFICATION OF RADIOSENSITIVITY OF BIOLOGICAL SYSTEMS
ORGANIZED BY THE
INTERNATIONAL ATOMIC ENERGY AGENCY
AND HELD IN VIENNA, 8–11 DECEMBER 1975

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FOREWORD

The treatment schedule of the radiotherapist has remained more or less unaltered during the last 30 years despite significant progress in the field of radiation biology. The radiotherapist, in fact, is overburdened with clinical work and rarely has enough time to think seriously about the new radiobiological concepts. He has adopted a pragmatic approach to his work and when he has had evidence of the efficacy of radiation treatment he has not delayed its application pending an agreement among radiobiologists on the theoretical principles behind it. When he has had a method of exposure that works, he has naturally shown little enthusiasm to change it.

Nevertheless, radiobiologists have continued to urge upon the clinician the need to try out their ideas, aimed at achieving better therapeutic results. They have suggested hyperbaric oxygen chambers and high LET radiations with a view to effectively destroying the hypoxic cells deeply embedded in the tumour. However, the giant accelerators and generators for producing high LET particles may prove too expensive for the developing countries. Under these circumstances, radioprotectors and hypoxic cell radiosensitizers may be useful alternatives. Whereas radiosensitizers would selectively enhance radiation damage to the cancerous cells, protectors can be used to minimize the harmful effects on the surrounding normal tissues.

The International Atomic Energy Agency has for some time been encouraging activities in this subject area. A panel of experts organized by the IAEA in collaboration with WHO discussed the radiosensitizing compounds in Stockholm in June 1973; the proceedings were published by the IAEA in 1974 under the title "Advances in chemical radiosensitization". The radioprotective compounds and their mechanisms of action had been discussed earlier at a panel held in Vienna in October 1968, the proceedings being published by the IAEA in 1969 under the title "Radiation damage and sulphydryl compounds".

New information has been accumulating which could be of particular relevance in the radiotherapy of cancer. New types of radiosensitizers and protectors have been discovered and the mechanisms of action have been better understood. Clinical trials initiated with some radiosensitizers have yielded encouraging results. It therefore seemed timely to discuss and evaluate these results with a view to providing guidelines for future research, and an Advisory Group on the Modification of Radiosensitivity of Biological Systems was called together by the IAEA in Vienna in December 1975. The papers presented as well as the conclusions and recommendations of the Group are included in the present Proceedings.

CONTENTS

A RADIOTHERAPIST'S VIEW OF RADIOSENSITISERS

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Abstract

A RADIOTHERAPIST'S VIEW OF RADIOSENSITISERS.

Various approaches to the combination of drugs with radiation with the intent of producing a potentiating effect on tumour cells are discussed. The importance of consistent sensitisation of tumour tissue as opposed to normal tissue is emphasized. The possibilities of achieving a useful therapeutic gain factor for combined treatment with halogenated pyrimidines, electron-affinic hypoxic cell sensitisers, ICRF 159 and bleomycin are reviewed.

1. INTRODUCTION

Radiosensitisers have been the subject of numerous reviews [1-5] and of symposia [6-7]. The current panel will discuss a limited number of topics and this introductory paper is intended to define certain principles concerning the clinical use of such agents.

The treatment strategy of a radiation oncologist when faced with a cancer patient will depend on what he knows about the natural history of the particular type of tumour in terms of spread; the extent at the time of presentation; its known response to therapy and the general physical status of the patient. Thus diseases may conveniently be divided into two groups determined by their natural history. There are types where metastases occur early, such as with most lung cancers, bone sarcoma and many poorly differentiated tumours. In this group of patients the strategy for cure will not only depend on the ability to control local disease but also to influence the metastatic growth by adjuvant therapy using chemotherapeutic agents and, more speculatively, by immunotherapy or hyperthermia.

The other group of patients in which the disease remains localised for some time is the one in which radiotherapists and surgeons are most able to effect cures. There is still, however, around one third of patients with cancer who die with disease as a result of local treatment failure rather than because of distant spread. Methods of improving local control in these diseases by radiotherapeutic potentiation would therefore have a considerable impact in terms of total number of patients.

However, in spite of this rather arbitrary division of patients into two groups, one should not rule out completely the value of radiotherapeutic potentiation in diseases with a high metastic potential. Especially if it is also possible to treat the metastases successfully with chemotherapy. Thus effective prophylactic chemotherapy for osteosarcoma has been found which may well now influence the prognosis of this disease. Treatment with methotrexate and adriamycin and with other adjuvant agents, may eliminate occult metastases if given early enough [8-9]. Osteogenic sarcoma has usually been regarded as radioresistant and therefore surgical ablation is the primary treatment. However, radiotherapeutic cures are possible and have been reported in

around 10% of cases {10}, this treatment usually being given because the tumour was not at a suitable site for amputation or surgery was refused. Most however fail to be controlled locally by radiotherapy. Goffinet and his colleagues {11} have reported 3 patients treated by radiotherapy following pulsed radiosensitisation with BUdR and associated with adjuvant chemotherapy. It may be that by using such techniques an improvement in local control will be obtained which, together with the adjuvant chemotherapy, will enable cures of osteosarcoma without limb ablation.

The groups of mechanisms by which drugs may produce an enhanced radiation effect on cells were defined in the conclusions of the previous panel {7}. In addition to these direct actions of drugs, one might also include other situations such as a drug which improves the abnormal tumour vasculature, as has been suggested for ICRF 159 {12-13}; or careful scheduling of a cytotoxic drug to produce shrinkage in a tumour associated with re-oxygenation, at which time radiotherapy should be more effective.

Many examples of drug and radiation combinations however only result in an adjunctive effect with an equal response of both tumour and normal tissue {5}. In the past too much attention has been paid to combinations of treatment which demonstrate radiosensitisation with scant regard for any adverse potentiation of the effect on normal tissues. The radiotherapist is not so worried about the technical problems of delivering enough radiation to a tumour to ablate it, unless this dose is accompanied by undue complications. Rads are inexpensive, patients are more precious.

We know that over a critically small dose range, relatively small increases in radiation dose may produce a considerable increase in cure rate {14-15}. A small potentiation of the radiation effect might then produce a disproportionate increase in cure rate. Unfortunately, the complication rate usually has a similar sigmoid shape. It is this relationship of the curve for tumour ablation and that for normal tissue complications which determines the clinical feasibility of radiotherapeutic cure.

The series of dose-response curves in Figure 1 is a theoretical representation of what might happen when radiosensitisation is attempted. Ideally one wishes to separate the response curves for tumour ablation and normal tissue complication rates so that there is no overlap, as in Fig. 1c. Merely to shift the curves equally to the left along the axis as in Fig. 1a will only save rads but not result in an improved therapeutic gain factor, as a given percentage of cures will still be associated with the same percentage of complications.

An adverse situation may occur if there is selective sensitisation of already sensitive tumour and of all the normal tissue cells, leaving resistant components of the tumour unsensitised. This might then result in curves like those seen in Fig. 1b.

It is therefore important to consider types and schedules of radiosensitisers and radioprotectors which are as fail safe as possible. If one is not going to do much good, at least one needs to be reasonably certain that not much harm will be done. Therefore in this context sensitisers of radioresistant components in tumours - such as hypoxic cell sensitisers, or protectors of euoxic cells are the most attractive current concepts.

The above considerations look at tumour ablation and normal tissue complications as abstract phenomena. Radiation therapists are concerned with the attempted cure of a volume of tumour contained within a viable host. The term complication may then cloak a variety of clinically acceptable or unacceptable situations. The volume of tissue treated must also be considered. Major complications in a small volume of tissue may not be as troublesome as less serious complications throughout a larger volume.

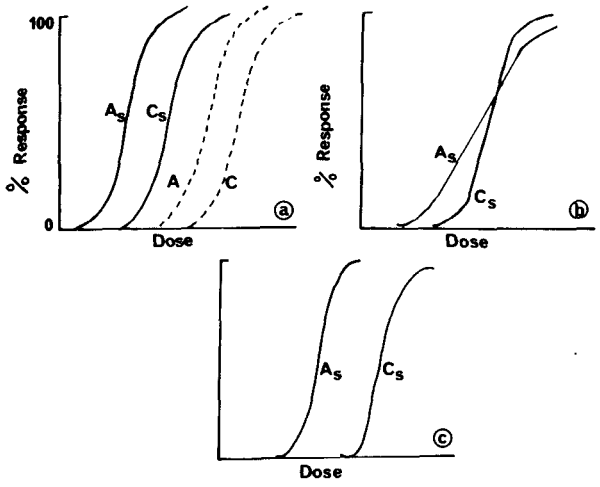

FIG. 1. Theoretical curves for tumour ablation and normal tissue complication rates with increasing radiation dose.

A = tumour ablation

C = normal tissue complication

A_C, C_S = rates with sensitiser

(a) Equal effect of sensitiser on tumour and normal tissue.
(b) Variable effect of sensitiser on tumour.
(c) Marked effect of sensitiser on tumour only.

The clinician might therefore find some sensitisation of normal tissue acceptable in a small volume with attendant complications, if it also results in tumour ablation. However in the larger tumour, when a larger dose to control 90% of the tumours (TCD_{90}) might be expected {16}, normal tissue sensitisation would be wholly unacceptable because of the volume of damaged normal tissue.

2. HALOGENATED PYRIMIDINES

The group of drugs most extensively investigated in man as chemotherapeutic and radiosensitising agents are the halogenated pyrimidines and their nucleosides {1, 2, 17}.

None of the major clinical studies provide convincing clinical evidence of potentiation when 5-Flurouracil is used in conjunction with radiotherapy. Other halogenated pyrimidines may act as true radiosensitisers and there have been clinical trials utilizing 5-BUdR or 5-IUdR at several different tumour sites {1, 5}. Results have been variable, and the results so far with halogenated pyrimidines do appear therefore to be disappointing. Perhaps, with careful selection of regional disease accessible to arterial perfusion and suitable scheduling of the sensitisers as proposed by Brown and his colleagues {18} this technique may be of some limited value.

3. HYPOXIC CELL SENSITISERS

I should now like to turn to another topic which to me is perhaps the most exciting one for clinical radiotherapy at this time. Certain electric affinic substances may selectively sensitise hypoxic cells without any sensitisation of the normal cells {4}.

Two most promising drugs that have been particularly investigated are Metronidazole and a Roche product which is known by the code of Ro-07-0582. Both these agents are relatively non-toxic to cells in vitro and can be given in high doses to animals and man {19, 20}. Metronidazole given in large doses by mouth may approach the same peak serum concentration as that required to achieve sensitisation in mouse tumours {21}. The drug is relatively nauseating but no untoward toxicity in man has been demonstrated, from large single doses. Successful phase I studies for repeated doses of Metronidazole have also recently been reported {22}. Radiotherapeutic studies have been commenced using it but no definite conclusions have yet been reported, although no evidence of adverse normal tissue effect has been observed.

Considerable interest now is centred around one of the 2-nitroimidazoles. Ro-07-0582 has been shown, in a variety of systems, to be even more effective as a sensitiser of hypoxic cells than Flagyl and like it, also to be relatively metabolically stable {19}. We {23} have found an enhancement ratio of 2.2 using the EMT6 mouse mammary tumour treated in vivo with a single fraction of radiation (Fig. 2). The animals were given 1mg/gm of Ro-07-0582 by the intraperitoneal route, 30 minutes before irradiation. Of course, if one can achieve adequate reoxygenation employing suitably fractionated radiation, this sensitisation then becomes less significant.

It is too early to bring this drug into routine clinical practice but the animal {19} and preliminary clinical results to be reported later {20} do lead one to hope that this might prove to be a useful agent.

4. ICRF 159

A chemotherapeutic agent of recent experimental interest is a bisdioxopiperazine, ICRF 159, {24} synthesised in the laboratories of the Imperial Cancer Research Fund, London. This bisdioxopiperazine has been reported to be a potent inhibitor of DNA synthesis and also to block progression through the cell cycle. Its effect is probably confined to one part of the cell cycle - the transition between G_2 and M.

Its usefulness in man for cancer chemotherapy used as a single agent has been disappointing because of its toxicity to normal tissues. However, its interest for radiation therapy lies in other properties of its action. It has been shown to induce changes in the blood vessels of some tumours, resulting in normalisation of the previously abnormal tumour vasculature {25}. This may then, as in experiments with the Lewis lung tumour, be associated with a reduction in the number of metastases. The drug has been shown to have some potentiation of the effect of radiation on the S180 tumour in rats {12}. However in vitro treatment of HeLa cells by ICRF 159 immediately followed by X-radiation failed to demonstrate any such radiosensitisation {26}. It has therefore been concluded that some at least of the in vivo radiosensitisation with the S180 tumour might have been associated with a normalised blood supply and improved oxygenation {12}.

Other workers {13} have similarly studied the Walker 256 carcinosarcoma and found an increased effect of the combination of ICRF 159 and radiation, but could not exclude an additive effect.

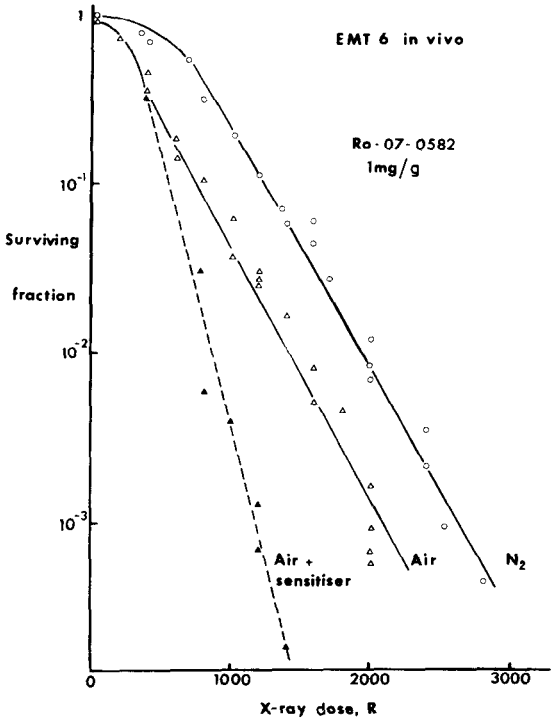

FIG. 2. Radiation dose response curve for EMT6 mouse tumour irradiated in vivo and assayed in vitro for surviving fraction.

○ *animals killed and irradiated in nitrogen*

△ *animals breathing air*

▲ *animals breathing air and given 1 mg/g of Ro-07-0582 intraperitoneally 30 min before irradiation.*

They quote data of Baungärtl and colleagues that the improved vascularisation following ICRF 159 treatment does lead to an increase in tissue pO_2, in this tumour.

Because of the possible clinical interest of this form of radiosensitisation we have been carrying out similar work and have been able to demonstrate a modest change in Do when exponentially growing EMT6 cells are exposed to the drug in vitro for 24 hours before X-radiation {27}. This effect is not seen with shorter drug exposures of 1 hour which probably explains Dawson's inability to demonstrate sensitisation in vitro. It does indicate that some radiosensitisation may occur without having to invoke improved oxygenation due to a change in tumour blood supply. Flow cytoflurographic evidence suggests that after 24 hours exposure to ICRF 159, there is a considerable build up of cells in G_2. This may be one explanation for the change in the Do at that time, although current work in progress leads us to doubt this as the sole explanation.

Several clinical studies are now in progress to test this possible synergism. Ryall and colleagues {28} reported on a series of 22 patients with soft tissue and bone sarcomas. They claimed better responses than could normally be expected. Severe toxicity resulting in interruption of treatment was not seen, although the skin reactions were greater than expected. The results of controlled clinical studies now in progress should show if this clinical impression is substantiated.

5. BLEOMYCIN

Yet another approach that has been investigated is the possibility that bleomycin might act as a radiosensitising agent. Bleomycin is known to inhibit DNA synthesis and to produce DNA strand breaks {29-30}. It has been suggested that it might have a synergistic effect on that of X-radiation { 5 }. This could be of particular value in those tumours where bleomycin is known to be useful in therapy, such as well differentiated squamous carcinoma in the head and neck region, or in those tumours where bleomycin has been reported to be selectively concentrated. This selective concentration of the drug could then provide an amplification factor for any possible radiosensitisation. Thus an increase in the concentration of radioactive bleomycin in an experimental mouse brain glioma over that in normal brain has been reported {31-32} .

There have been reports of responses of primary brain tumours to bleomycin used as a carcinolytic agent. In view of this, and the possibility of concentration in the gliomas of man, we studied the bleomycin concentration in biopsy specimens taken from patients with glioblastoma multiforme. When possible we looked at glioma tissue and a sample of normal brain which the surgeon removed during the approach to the biopsy excision. In all 5 patients, within the limitations of the microbiological assay method {33}, the glioma showed an increase in concentration of bleomycin of between 2-12 with a mean ratio of 5 times that of adjacent normal brain.

Unfortunately the investigations for possible radiosensitisation by bleomycin do not appear to give a clear answer either when using in vitro cell culture systems or following treatment of tumours in vivo.

We have studied the effect of the combination of bleomycin and X or gamma radiation in bacterial and two mammalian cell lines {34}. There was a marked sensitisation effect when using the radiation resistant E. coli B/r. However, this effect was only seen when the cells were exposed to the drug after the radiation and was not seen when the exposure to bleomycin was before or during the radiation treatment. This mutant has a high capacity for removing radiation induced DNA single strand breaks and it may be that bleomycin acts by reducing the repair capacity of this strain. No such potentiation effect was seen in two other bacterial strains used, E. coli B/s and Micrococcus radiodurans. Likewise no sensitisation was seen by us with two mammalian cell lines in vitro, HeLa and the EMT6 mouse mammary tumour.

Bienkowska and her colleagues {35} were unable to find any potentiating effect of bleomycin on X-radiation using HeLa cells in vitro. However, Matsuzawa and his colleagues {36} using a mouse mammary carcinoma line showed what appears to be a reduction in the shoulder width, and possibly in the slope, after pretreatment of the cells for 1 hour with a dose of bleomycin which causes a small amount of cell killing (around 10%). In view of the small changes seen their conclusions must be regarded with some caution.

The results of in vivo experiments are also contradictory. Jørgensen {37} presented experimental evidence that a squamous carcinoma in mice may be controlled more successfully when bleomycin

is added to the radiotherapy. Radiation alone produced a 70% reduction of tumour growth in a 3/52 period after treatment. The combination treatment with bleomycin resulted in over 95% regression. However, no indication was given of any local increase in reaction in the skin, and there is no evidence therefore that any useful gain factor was obtained. In contrast, Sakamoto and Sakka {38} were unable to demonstrate any sensitising effect on the radiation response of a murine squamous carcinoma treated in vivo and assayed by the TD_{50} dilution assay method.

In spite of this experimental evidence there are numerous reports of the continued use of radiotherapy together with bleomycin in treatment, principally for squamous carcinoma in the head and neck region. There are enthusiastic results claimed but they are difficult to evaluate in the absence of suitable controls. The Medical Research Council in the United Kingdom is now carrying out a controlled trial to investigate this problem.

CONCLUSIONS

This paper summarises a few of the possible approaches to radiosensitisation that are now being investigated. These and others are the subject of more detailed analysis in subsequent papers presented at this panel. The great problem for the radiotherapist with most studies previously reported has been the lack of tumour specificity. There are experimental and early clinical indications that this goal may now be in sight.

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RADIATION MODIFIERS
An evaluation of recent research and clinical potential

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Abstract

RADIATION MODIFIERS: AN EVALUATION OF RECENT RESEARCH AND CLINICAL POTENTIAL.

Although radiation-modifying agents have made significant contributions to our understanding of basic radiobiological mechanisms, their impact on clinical radiotherapy has been limited. Recent developments in protection and sensitization, however, have raised new hopes that some of these agents may soon find a place in therapy and have enticed a number of researchers and clinicians to seriously evaluate this possibility. The paper reviews these recent developments, with emphasis on work in the United States, and makes recommendations for experimental areas and approaches which appear to have considerable promise – in particular, combinations of sensitizing and protective agents, of sensitizers that act by independent mechanisms, and of modifying agents and other treatment modalities. It is concluded that intensification of basic efforts, in conjunction with well-designed and carefully evaluated clinical trials, could lead, within a relatively short time, to a definitive evaluation of the importance of anoxic cells in human radiotherapy and to a significant clinical role for radiation-modifying compounds.

I. INTRODUCTION

For more than twenty-five years, scientists in many countries have studied chemical compounds that modify the effects of ionizing radiation on biological systems. Although these studies have contributed significantly to our basic knowledge about radiation effects, they have not yet had an impact on cancer radiotherapy and, until fairly recently, the majority opinion was that they never would. For whatever reasons, interest in the area flagged and many workers turned to less frustrating interests.

In recent years, this trend has been dramatically reversed and the chemical modification is now enjoying something of a renaissance. Subjectively, all of us who referee for scientific journals are aware that the number of manuscripts in radiation modification grows larger each month. In more objective terms, the rate of publication in the field provides a good indicator of this trend: Figure 1, for example, documents the intense activity generated through the 1960s and the slump that followed. However, when one examines the year-by-year publication of papers in only biological areas, it is apparent that both protectors and sensitizers are enjoying a resurgence of interest (see Figure 1). With this renewed interest has come renewed hope for eventual clinical applications.

This meeting provides a unique opportunity to assess the present "state of the art" and to make recommendations for future directions. It is particularly appropriate that we have been convened by the IAEA, because of the great potential contribution to this area of research by scientists and clinicians in less developed nations, who may not have ready access to facilities such as neutron generators.