PART I: INTERACTION OF RADIATION WITH DRUGS. ABSTRACTS OF SYMPOSIUM PAPERS
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TEMPORAL ASPECTS OF DNA REPAIR PROCESSES AFTER DRUGS AND RADIATION. B. W. Fox, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester.

Before considering the ultimate effect of drug and radiation in combination on biological end points such as cell cycle phase parameter changes, mutation frequency and eventually survival, it is desirable to know what sequence of changes may be expected following the drug or radiation treatment alone. The timing of events within the cell attempting to overcome damage to its DNA will depend on (a) the nature and multiplicity of the lesions produced on the DNA, (b) the genetic competence of the cell to undertake the different types of repair required by such lesions, (c) the conditions under which the cell is growing which may favour or hinder different repair mechanisms and (d) the efficiency of each repair event in restoring the full competence of the original DNA in its transcriptional and replicative roles. Difficulties experienced during these events may determine the subsequent fate of the cell. These difficulties result from a subtle interplay of dose–time relationships of the characteristic biochemical disturbances exerted by each agent. An attempt has been made to understand the interplay of some of these events using alkylating agents such as methyl methane sulphonate and methyl-nitro-nitrosoguanidine and comparing them with both x-rays and ionizing radiation. The present status of such studies designed to rationalize combination treatment could not be considered to do more than influence to a small extent an otherwise empirical approach to combination treatment.

EFFECTS OF DAUNOMYCIN, BLEOMYCIN, CYTOSINE ARABINOSIDE, ACRONYCINE AND IONIZING RADIATION ON THE CELL CYCLE *IN VITRO* AND *IN VIVO*. W. A. Linden, S. B. Reddy and F. Zywietz, Institut für Biophysik und Strahlenbiologie der Universität Hamburg.

Four chemotherapeutic agents without, or in combination with, 200 kV x-rays were examined for their influence on cell cycle progression and viability of mouse L-cells. The action of daunomycin and ionizing radiation was also tested on the Walker carcinoma *in vivo*. The cell kinetics after different treatments were studied using the technique of pulse cytophotometry. By this method, DNA distribution patterns (DNA histograms) of the cells were obtained. The mathematical analysis of the DNA histograms yields the fractions of cells in G_1, S and G_2 or M. Cytosine arabinoside predominantly blocked the cells in S phase while daunomycin, bleomycin and acronycine accumulated the cells in $(G_2 + M)$-phase. These results vary in combination with irradiation.

EFFECTS OF INTERACTIONS OF CELL CYCLE-SPECIFIC CYTOTOXIC DRUGS AND X-RADIATION ON SURVIVAL OF CELL REPRODUCTIVE CAPACITY. R. J. Berry, MRC Radiobiology Unit, Harwell.

Cells of murine leukaemia P-388 *in vivo* and HeLa cells *in vitro* have been used for several years to study interactions between effects of cytotoxic chemotherapeutic agents, including halopyrimidines and folic acid antagonists, and subsequent survival of cell reproductive capacity after x-irradiation. Using these latter classes of drugs as specific examples, combination of information on drug radiation interactions with even our limited knowledge of cell proliferation kinetics in tumours and dose limiting normal tissues allows some predictions to be made about effects of the sequential and concomitant use of cytotoxic drugs with conventional and unorthodox dose fractionation in radiotherapy.

EFFECTIVENESS OF COMBINED TREATMENTS OF VARIOUS TYPES OF TRANSPLANTABLE RAT TUMOUR WITH IONIZING RADIATION AND DRUGS. G. W. Barendsen, A. F. Hermens and H. C. Janse, Radiobiological Institute TNO, Rijswijk.

Many tumours in animals and man contain, in addition to proliferating (P) cells,

non-proliferating (Q) cells, which may differ in their sensitivity to drugs or ionizing radiation. Experimental data on changes in cell proliferation characteristics of a transplantable R-1 rat rhabdomyosarcoma have shown that the fraction of P cells may increase and the cell cycle time may decrease after irradiation. This has led to experiments on the effectiveness of a cell cycle-specific drug given at various time intervals after irradiation.

Growth delay of the R-1 rhabdomyosarcoma was measured after doses of 2000 rad or 1000 rad of x-rays, followed at intervals of up to 12 days by the administration of vinblastine at a dose level of 1·5 mg/kg of body weight. This dose of vinblastine alone induced a growth delay of 2.5 days, while 1000 rad and 2000 rad of x-rays induced growth delays of 7 and 15 days respectively. Vinblastine given 8 h before irradiation gave approximately the same effect as irradiation only, but vinblastine given 48–192 h after irradiation caused a very significant excess delay of about 8 days over that expected from a directly additive action. This can be ascribed to recruitment of Q cells into the compartment of P cells. A similar synergistic effect was observed for a rat osteosarcoma but not for a rat skin carcinoma and a rat bladder carcinoma.

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IN VIVO INVESTIGATIONS ABOUT THE EFFECTS OF RADIATION AND/OR DRUGS IN NORMAL TISSUE AND IN SARCOMA-180. W. PORSCHEN and L. E. FEINENDEGEN, Laboratory of Neutron Biology and Cellular Tumor Kinetic, Institut für Medizin, KFA, Jülich.

An external assay has been developed and modified in this laboratory that permits the evaluation of the effects of radiation and/or drugs in the living mouse. Cells are labelled *in vivo* with iododeoxyuridine (^{125}IUdR). IUdR is an analogue of thymidine; both precursors are specifically and rapidly incorporated into DNA of S cells at the time the precursors are made available. Reutilization of IUdR is minimal; therefore labelled IUdR is the tracer of choice for turnover studies. The soft γ-rays from ^{125}I are easily measured externally, either with the whole body counter or with a tumour measuring device specifically developed for assaying solid tumours.

This paper reports on the effect of radiation and/or drugs on the rate of incorporation of ^{125}IUdR into whole body DNA and tumour DNA in the living mouse. In addition, the effect of actinomycin D on the rate of turnover of labelled tumour cells in the living mouse was assayed. Prolonged observations in the living organism with this technique do not disturb the physiological equilibrium, be it in normal or in tumour bearing animals. In this study, sarcoma-180 was used as a solitary tumour growing in the hind leg of NMRI mice; 10–12 mice were used per experimental point.

The incorporation of ^{125}IUdR into whole body DNA on one hand and tumour DNA on the other hand was measured in the living mice at various times after acute exposure to γ-radiation, neutron radiation or after a single administration of fluorouracil, hydroxyurea and actinomycin D. Each of these treatments caused a specific effect of different duration and the maximum effect in the whole body surpassed that observed for the tumour. On the other hand, a single administration of a platinum complex compound (cis-dichloro-diammine-platinum) caused not only prolonged effects in the whole body and tumour but the effects to the tumour surpassed that of the whole body: combined effects of actinomycin D and radiotherapy on sarcoma-180 were different from those seen in the whole body. In both instances, the additional effect of actinomycin D resembled the maximal effect of either treatment alone. It was found that actinomycin D enhanced the radiation effect on tumour growth when it was given 3–4 h either before or after irradiation. Actinomycin D treatment or combined therapy indicated that actinomycin D alone had little effect on cell loss rate from labelled tumours. Combined therapy did not significantly alter the increased rate of cell loss observed for radiotherapy alone, yet combined therapy appeared to cause the enhanced cell loss rate to be prolonged in comparison with radiotherapy alone.

COMBINED EFFECT OF 5-FU AND ^{60}CO ON INTESTINE, BONE MARROW AND ON TRANSPLANTED TUMOUR IN MICE. A POSSIBLE