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 (125IUDR). 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 125I 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 125IUDR 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 125IUDR 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 60CO ON INTESTINE, BONE MARROW AND ON TRANSPLANTED TUMOUR IN MICE. A POSSIBLE
DIFFERENTIAL EFFECT BETWEEN THESE TISSUES RELATED TO DRUG AND GAMMA-RAY FRACTIONATION SCHEMES. A. WAMBERSIE, H. MAISIN, M. VAN DER PERRE and M. R. SMOES, Radiotherapy Unit, Tumour Centre, Capucienenvoer, Louvain.

Combination of irradiation and 5-FU was proved clinically to be of interest in the treatment of malignant tumours, in particular of the gastrointestinal tract. The possibility of achieving a differential effect between several tissues as a function of fractionation of drug and irradiation ($^{60}$Co) was investigated.

Three biological criteria were studied in mice: intestinal death (LD$_{50/3}$) after abdomen irradiation, bone marrow death (LD$_{50/30}$) after total body irradiation and the response of a Landschut tumour grown in a solid or ascitic form. Total 5-FU doses of 75 or 150 mg/kg were administered i.p.

For LD$_{50/3}$, 5 equal daily injections, on Day 5 to 1 before irradiation, were more efficient than a single injection 3 days before irradiation. The contrary was observed for LD$_{50/30}$, suggesting a differential effect between these 2 normal tissues related to 5-FU fractionation. The first results on Landschut tumours are similar to those observed for LD$_{50/3}$. On the investigated tissues, 2 i.p. injections of 5-FU 18 and 9 h before irradiation were less efficient.

D$_2$–D$_1$ was studied for an interval of 3 1/2 h, 24 h and 4 days between the fractions of $^{60}$Co. For LD$_{50/3}$ and LD$_{50/30}$, D$_2$–D$_1$ was not significantly reduced after 5 injections of 5-FU (75 mg total dose) taking into account the reduction of size of the gamma fractions.

RADIATION AND DRUGS; VARIOUS MECHANISMS OF INTERACTION.

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Various mechanisms were studied in which combination of radiation and drugs could be more effective than adding more radiation, and model systems were developed to identify these mechanisms.

Interaction of drugs and radiation leading to sensitization could occur through one of the following mechanisms: (a) interaction due to presence of the drug during exposures, (b) interference with repair, (c) differential effectiveness of drugs on tumour and host cells through different degrees of cell kinetic response to radiation (recruitment) in these 2 systems.

The mechanism of type (a) was studied for hypoxic sensitizers on a poorly reoxygenating mouse osteosarcoma. It was found that metronidazole and Ro-07-0582 had a more than additive effect on this tumour when combined with fractionated radiotherapy. Mechanisms of type a, b and c were studied in normal mouse haemopoietic stem cells. None of the agents tested was effective by mechanism (a) on well oxygenated haemopoietic stem cells. For 5-FU and vinblastine an effectiveness by mechanism (b) could be confirmed and many drugs were effective by mechanism (c). However, the limitation of the analysis to normal tissue made it impossible to identify a gain of effectiveness on tumours compared with normal tissues.

It seems unlikely that all clinical tumours may be influenced equally by combination therapy and it will be necessary to identify the various categories of tumour radiation resistance in order to apply the optimal type of combination therapy.

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PART II

ABSTRACTS OF PROFFERED PAPERS

RADIOPROTECTIVE EFFECT OF WR 2721 IN COMBINED INJURED MICE (X-IRRADIATION AND SKIN LESION), F. VERSPOHL and O. MESSERSCHMIDT, Laboratorium für Experimentelle Radiologie, Neuherberg bei München.

The protective effect of the thiophosphate compound WR 2721, resulting in a reduction of radiation lethality in mammals, is well known. The effectivity of protective agents after infliction of irradiation and an additional wound or other kind of stress on animals has not yet been investigated.

In our investigations female mice were given x-irradiation and an open dorsal wound was made 2 or 8 days after irradiation.