Pituitary Effect on Synthesis of Deoxyribonucleic Acid in Regenerating Rat Liver following Whole-body X-irradiation

WHOLE-BODY X-irradiation delivered within 6 hr. of hepatectomy will inhibit the synthesis of deoxyribonucleic acid (DNA) in regenerating liver. This inhibition has been elegantly demonstrated to be a result of the failure to synthesize certain enzymes concerned with the formation of DNA[1]. The nature of this inhibition of enzyme formation is suggested by two recent reports. Myers[2] has reported that synthesis of DNA in regenerating liver is not completely inhibited following X-irradiation of liver only, and Benjamin and Yost[3] have observed that the uncoupling of oxidative phosphorylation seen in liver mitochondria following whole-body irradiation is due to a pituitary stimulation with subsequent activation of the adrenal cortical hormones. These observations suggest that this interesting and rather unusual effect of low doses of whole-body X-irradiation on synthesis of DNA in the intact animal may be due to a pituitary stimulation which ultimately results in a decreased amount of energy being available for enzyme synthesis. The possibility of a pituitary effect on synthesis of DNA in regenerating liver following whole-body X-irradiation was confirmed in the experiments reported here.

Male Sprague–Dawley rats (180–200 gm.) underwent partial hepatectomy by a standard method[4], and then were irradiated within 2 hr. of the operation. The animals were given 15 μc. radioactive phosphate intraperitoneally 3 hr. before they were killed (see Table 1 for schedule). Following killing, the livers of all animals within a group (2–3) were pooled, the DNA isolated, and the specific activity determined as suggested by Hecht and Potter[5]. All irradiated animals received 750 r. delivered by a General Electric 'Maxitron 250' operated at 30 m.amp., 250 kVp. with added filtration of 1 mm. aluminium, 0·5 mm. copper, delivering 106 r./min. at 50 cm. Shielding of animals was accomplished in a restraining box covered with 1·5 cm. lead located outside the radiation beam.

The results of these experiments are summarized in Table 1.

Table 1. SPECIFIC ACTIVITY OF DNA ISOLATED FROM REGENERATING RAT LIVER FOLLOWING VARIOUS RADIATION PROCEDURES

Procedures	Time after death (hr.)	Specific activity (c.p.m./mgm.)
Non-irradiated	18	0
Non-irradiated	22	777
Whole-body	22	0
Head only	22	0
Body only	22	38
Body only + 10 units of adrenocorticotrophic hormone	22	0
Body only + 1 unit of thyroid stimulating hormone	22	0

These experiments show that under conditions in which synthesis of DNA is active (19 hr. postoperative), 750 r. delivered either to the whole body or to the head will suppress synthesis of DNA in regenerating liver. Head shielding resulted in a markedly reduced synthesis and the administration of pituitary hormones immediately following irradiation further abolished DNA synthesis. The reciprocal experiments were also tried using commercial hypophysectomized rats but none of these animals survived the course of the experiment. The conclusion from this series of experiments is that irradiation of the head alone produced the same inhibition of DNA synthesis in regenerating liver as irradiation of the whole body, and that DNA synthesis, although reduced, was present when the head was shielded. The reduction of DNA synthesis in animals with their heads shielded may be the result of adrenal stimulation following X-irradiation.

In view of the importance of regenerating liver as a system for studying synchronous formation of DNA, these experiments serve as a reminder that contributions from other organs in modifying synthesis of DNA in liver should not be ignored. This is especially true in radiation work on synthesis of DNA as well as on population changes in 'radiation-sensitive' tissues.

This work was supported by a United States National Health Service grant 3925 (c–2).

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[1] Bollum, F. J., Anderegg, J. W., McElya, A. B., and Potter, V. R., *Cancer Res.*, **20**, 138 (1960).
[2] Myers, D. K., *Canad. J. Biochem. Physiol.*, **38**, 1059 (1960).
[3] Benjamin, T. L., and Yost, H. T., *Rad. Res.*, **12**, 613 (1960).
[4] Higgins, G. M., and Anderson, R. M., *Amer. Med. Assoc. Arch. Pathol.*, **12**, 186 (1931).
[5] Hecht, L. I., and Potter, V. R., *Cancer Res.*, **16**, 988 (1956).

Radioprotective Effects of Reserpine and its *N*-oxide

CERTAIN amine oxides exert a protective effect against radiation injury[1,2]. Reserpine has also been shown to have this action[3]. This suggested a comparison between reserpine and its *N*-oxide. Groups of 20 *CF*–1 mice were administered various doses of the two compounds 24 hr. before X-irradiation with 600 r. (Table 1). Radiation conditions were the same as described previously[1]. Both compounds produced typical reserpine effects, sedation and ptosis, but the *N*-oxide was less active per dose. All three doses of reserpine *N*-oxide significantly increased the ST_{50} day, whereas only one dose of reserpine had this effect (Table 1). On the basis of total survival it requires twice as much reserpine as its *N*-oxide to decrease mortality by 25 per cent, and neither compound is as effective as quinoxaline di-*N*-oxide[1] or anhydroerythromycin *N*-oxide[2]. Mechanisms of action are probably different, since the reserpine compounds exert no antibiotic effects. However, they have the proper chemical structures postulated for removing oxidizing radicals[2]. Protection might be partially the result of the release of known protective compounds, adrenaline and 5-hydroxytryptamine[5]. The release of catecholamines and 5-hydroxytryptamine is essentially complete 16 hr. after reserpine administration, and the binding sites, as well as the plasma content, do not begin to contain appreciable amounts of these amines for at least 4 days[6–9]. Metabolism and excretion are also going on at this time, and in all probability the amount of such amines available for exerting a protective effect is below that necessary for such an action. On the other hand, reserpine has been found in body tissues for at least 48 hr. following a single dose[10]. Most of the reserpine was found in the tissue cells where, in the present radiation experiment, it could act as a protecting compound. The fact that reserpine and its *N*-oxide exert only a slight protective effect against