sated animals after far-lateral hypothalamic stimulation, although pure feeding responses are obtained. Thus basic feeding responses occur without the bundle but the animal will not "work" for its food. Since stimulation of the feeding and satiety areas simultaneously produces feeding in sated animals but not grill-running to lever-press for food, it seems likely that the "satiety brake" is acting on the medial forebrain bundle "motivational system" and not on the far-lateral hypothalamic basic feeding mechanisms. These results probably indicate the presence of motivational elements in the medial forebrain bundle necessary for "hunger drive" which are selectively suppressed by the "satiety" center. The far-lateral hypothalamic area would thus seem to contain the basic elements concerned directly with activation of specific feeding reflexes. It is concluded, therefore, that the "feeding" center probably is composed of both basic "feeding" and "hunger drive" elements, only the latter being depressed by the satiety mechanism (6).

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Radioprotection by Mitotic Inhibitors and Mercaptoethylamine

Abstract. In the mouse, chemical interference with cellular proliferation alters the radiosensitivity of the bone marrow, and this results in protection from otherwise lethal x-irradiation. When intestinal damage is minimized by appropriate timing and dosage, many mitotic inhibitors increase radioresistance and enhance the protective effects of mercaptoethylamine.

It has been postulated that radioprotective chemicals operate by way of tissue hypoxia, inactivation of free radicals, or by the formation of mixed disulfides, or by all three (*1*). However, such mechanisms fail to explain the delayed protection against lethal radiation reported by Smith (*2*) for a colchicine derivative, or by Cole (*3*) for urethan. These latter agents have at least one common feature. That is, correct dosage results in mitotic inhibition followed by changes in cellular proliferation (*4*). With this feature as a working hypothesis, we have studied the effect of a series of mitotic inhibitors upon the radiosensitivity of mice. Preliminary results allow us to describe the action of a large class of radioprotective agents both singly and when combined with mercaptoethylamine, a known radioprotective compound.

Table 1. Survival data of mice receiving single large doses of mitotic inhibitors, alone and combined with mercaptoethylamine. Individual results represent groups of ten treated and ten control animals exposed to lethal x-irradiation.

Inhibitor	Intraperitoneal administration prior to x-ray		800 r 30-day survival (%)	
	Dose (mg/kg)	Time (hr)	Agent alone	Agent plus MEA*
	Metaphase inhibitors			
Colcemide	50	1	50	100
Colcemide	50	12	0	30
Colcemide	50	48	20	100
Sodium arsenite	12.5	24	40	100
Cadmium chloride	2.5	24	10	70
	Preprophase inhibitors			
Epinephrine	2	24	10	80
Urethan	1000	48	50	90
Cortisone	200	48	10	30
T-P vaccine†	†	24	10	100
	Mercaptoethylamine			
MEA	75	0.25	30	

* Mercaptoethylamine, 75 mg/kg, 15 minutes before x-ray. † Typhoid-paratyphoid vaccine (Pitman-Moore), 0.5 ml per mouse.

Young female mice (Bagg Swiss), weighing 20 to 25 g, were used. Equal numbers of control mice were irradiated simultaneously with each treated group and thereafter housed jointly. Irradiations were accomplished with a G.E. Maxitron unit: 300 kv; 20 ma; HVL, 2 mm Cu; TSD, 85 cm; dose rate, 45 r/min. The 800-r dose of x-irradiation was uniformly lethal in these experiments, all control mice dying before the 21st day after exposure.

The survival data in Table 1 show clearly that mitotic inhibitors are capable of decreasing the sensitivity of mice to lethal x-irradiation. Likewise, pretreatment with these agents enhances the radioprotective effect of a small dose of mercaptoethylamine. The cytotoxic action of the mitotic inhibitors has been documented adequately by Biesele (*4*).

Most mitotic inhibitors depress both the hematopoietic tissue and the gastrointestinal epithelium, but the time for maximum depression varies for each tissue. This variation allows one to achieve selective inhibition by proper timing and optimal drug dosage. It became evident early in the course of our studies that we must avoid a combination of chemical and radio-inhibition of the intestinal epithelium. Either injury causes some degree of cell depletion and tends to increase radiosensitivity. Combined inhibition leads to severe intestinal damage which is expressed clinically by diarrhea and death 5 to 8 days after 800 r of x-irradiation (*5*). The results obtained with colcemide (*6*) (Table 1) demonstrate a biphasic effect upon radioresistance, with loss of protection 12 hours after administration of the drug. This time-effect fits the response curve for colchicine-induced inhibition of the gut as reported by Friedman (*7*).

Our experiments suggest that proper timing in the use of mitotic inhibitors will permit selective alteration of the radiosensitivity of the bone marrow. This alteration is manifested by an increase in radioresistance, and by a greater response to the protective effects of mercaptoethylamine, as measured by 30-day lethality.

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