Effect of X-Ray Dose on Mortality and Skin Transplantability in Mice Receiving F_1 Hybrid Marrow.* (22674)

J. J. TRENTIN†

Department of Anatomy, Baylor University College of Medicine and University of Texas Dental Branch, Houston.

Mice receiving an otherwise lethal dose of X-irradiation, but protected with bone marrow from an F_1 hybrid derived from the irradiated and a foreign strain, will subsequently tolerate skin homografts from the F_1 hybrid or the foreign parent strain of the F_1 hybrid(1,2). Mice protected with marrow from the same (isologous) strain will not tolerate skin homografts from the F_1 hybrid or the foreign parent strain. The following experiments were undertaken to determine the lowest dose of whole body X-irradiation, followed by marrow from an F_1 hybrid, that would result in tolerance of skin homografts from the foreign parent strain. During the course of these experiments an entirely unexpected and interesting observation was made regarding mortality in marrow-treated mice at decreasing doses of irradiation.

TABLE I. Percent Mortality following X-irradiation.

	All strains combined			CBA strain		
		% mortality after indicated			% mortality after indicated	
Dose, r	No. of mice	No. of days 21	30	No. of mice	No. of days 21	30
330	22	0	0	12	0	0
400	12	0	0			
500	24	17	21			
550	54	9	9	24	12	12
600	36	64	67	12	50	50
660	84	93	94	48	90	90
700	24	100	100			
770	266*	99	100	60	100	100
800	50	100	100	11	100	100
1000	12	100	100			
1200	12	100	100			

* 159 of the mice at 770 r received intrav. saline inj. as controls for other groups receiving bone marrow suspensions.

Materials, methods and terminology are similar to those reported previously(2) with the following exceptions. One marrow donor

TABLE II. Mortality and Skin Transplantability in Unirradiated, X-irradiated and Marrow Treated CBA Mice.

									Skin graft				
Exp.	X-ray dose, r	Marrow donor	No. of mice	% mortality after indicated No. of days 12	21	30	60	100	Skin donor strain	No. of mice grafted	Days post-X-ray and/or marrow when grafted	No. of takes	No. of sloughs
A	0	Cb × CBA	12	0	0	0	0		Cb	12	46–52	0	12
	110	*Idem*	12	0	0	0	0		"	12	46–52	0	12
	330	"	12	0	0	0	0		"	12	46–52	0	12
	550	"	12	67	100	100	100	100		0			
	770	"	12	0	0	0	8*		Cb	11*	46–52	11	0
	0	None							CBA	13		12	1
B	660	Cb × CBA	12	0	0	17	42†	50	Cb	9	34–55	6†	0
	770	*Idem*	12	0	0	0	0	0	"	12	34–55	9	3
	660	None	12	67	100	100	100	100		0			
	0	"							Cb	9		0	9
	0	"							CBA	21		21	0

* One mouse in this group died the day following skin grafting and is excluded from the skin graft data but included in the mortality data.

† Three mice in this group died (one as a result of anesthesia during photography) with viable skin grafts 13 to 18 days after skin grafting. They are excluded from the skin graft data but included in the mortality data.

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TABLE III. Mortality and Blood Count in X-irradiated CBA Mice Receiving Cb × CBA F_1 Marrow.

Strain of mice	X-ray dose, r	Marrow donor	No. of mice	% mortality after indicated No. of days			Blood counts at 2 wk post-irradiation					
				12	21	30	No. of mice counted	WBC/mm³ Mean	WBC/mm³ Low	WBC/mm³ High	Million RBC/mm³ Mean	Million RBC/mm³ Low	Million RBC/mm³ High
CBA	330	Cb × CBA	12	0	0	0							
"	550	*Idem*	12	33	92	92	5	3,430	800	7,400	7.33	3.18	11.75
"	770	"	12	8	8	17	5	9,190	8,500	11,950	11.49	8.65	13.63
Balb/c*	770	None	12	100	100	100							

* Balb/c mice were used as an irradiation control because of a shortage of CBA mice.

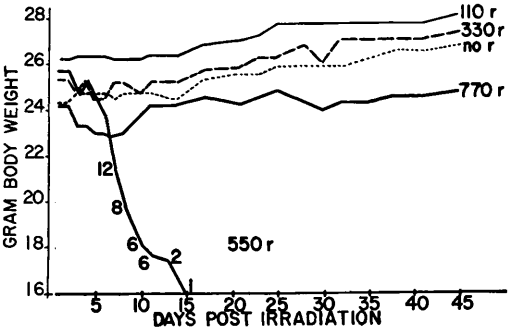

FIG. 1. Body wt data of Exp. A, Table II. All points represent mean wt of 12 mice with the exception of the 550 r group. Numbers along this line represent decreasing numbers of surviving mice at each point.

mouse was used for every 2 irradiated mice in Experiment A of Table II and in the experiment of Table III, rather than 1 for 1 as in previous work, including Experiment B of Table II. The intravenous injection volume was .5 cc throughout. The nucleated cell counts for the marrow suspensions used were 67,200, 89,150 and 61,250 per cu mm for Experiments A and B of Table II and for Table III respectively. Duco cement was applied to the sutured edges of the skin grafts of Experiment A, but not of Experiment B.

Observations. The 21-day LD_{50} of X-irradiation under the conditions used is about 600 r, while 770 r is uniformly lethal to all mice within 30 days (Table I) Mice of the CBA strain were equally distributed by age and sex into 5 treatment groups, each containing 12 mice. These groups received 0, 110, 330, 550, and 770 r of X-irradiation followed in 1 to 2 hours by intravenous injection of marrow from the Cb x CBA F_1 hybrid. As in past experience(2), F_1 marrow gave excellent protection against the otherwise lethal dose of 770 r (Experiment A of Table II). At the lower dose of 550 r, however, administration of the same suspension of hybrid marrow was followed by 100% mortality in 15 days. Body weight loss at 550 r was much more severe than at 770 r and was progressive until death (Fig. 1). Mice receiving still lower doses of irradiation or no irradiation, followed by marrow treatment, showed no mortality. At 46 to 52 days post-irradiation the surviving mice were homografted

with skin from the Cb strain, the other parent strain of the F_1 marrow donor. Of a group of 13 untreated CBA mice simultaneously autografted as controls, 12 of the autografts took. All of the homografts sloughed at the 0, 110 and 330 r dose levels. Of the 11 mice at 770 r that survived skin grafting, all of the foreign skin grafts were accepted and are in good condition 124 to 130 days after grafting. In previous experiments no late sloughs have been observed under similar conditions. Fifteen of 18 grafts at 660 and 770 r were successful and are still in good condition 130 to 152 days after grafting (Experiment B of Table II). In this earlier experiment it will be noted that late mortality in F_1 marrow protected mice at 660 r was greater than at 770 r. In both of these experiments mice receiving the different doses of irradiation were caged separately, 6 to a pen. It is therefore possible that an undetected infectious agent may have involved the 4 pens of mice at 550 and 660 r to account for the greater mortality at these levels than at 770 r. To control this possibility another experiment was set up in which mice receiving 330, 550 and 770 r followed by Cb x CBA marrow were caged together, 2 at each dose level in each pen of 6 mice. Again the mice at 550 r showed much higher mortality than their cage mates at 330 and 770 r (Table III). Body weight loss at 550 r was much greater and more progressive than at 770 r. Blood counts performed 2 weeks post-irradiation showed a significantly lower white and red cell count in the mice at 550 r than in those at 770 r. Platelets were less numerous in the stained blood smears of the mice at 550 r than in those at 770 r.

Discussion. The blood count data suggest that the greater mortality at 550 r than at 770 r may be related to a less adequate hematopoietic recovery. On the other hand, 550 r without bone marrow had earlier resulted in 30-day mortality of only 12% of 24 CBA mice and 9% of 54 mice of all strains combined. Additional experiments are obviously indicated, and no explanation of the mechanism involved will be ventured at this time.

Summary. The 21-day LD_{50} under the conditions of X-irradiation used is approximately 600 r. Irradiation of CBA mice followed by intravenous administration of bone marrow suspension from Cb x CBA F_1 hybrids resulted in little or no 21-day mortality at 110, 330, 660 and 770 r, but in almost 100% mortality at 550 r. Homografts of Cb skin into the surviving mice were accepted by the mice at 660 and 770 r dose levels but not by mice at 0, 110 and 330 r dose levels. None of the marrow-treated mice at 550 r survived long enough to be skin grafted.

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Effect of Chlorpromazine on Excretion of 5-Hydroxyindoleacetic Acid in a Patient with Malignant Carcinoid. (22675)

JACK W. COLE AND GEORGE G. BERTINO.

The Department of Surgery, Western Reserve University, School of Medicine and University Hospitals of Cleveland, Cleveland, Ohio.

Since the first authentic case report of Beger(1) in 1882 of a carcinoid of the appendix the tumor has been of interest to the clinician principally because of its rarity and to the histologist because of its unusual cell type and staining properties. Gosset and Masson(2), using silver impregnation technics, demonstrated the presence of intracytoplasmic granules which stain black with silver and which were indistinguishable from the granules found in the argentaffin cells of the intestinal mucosa. Masson suggested the possibility that carcinoid tumors arise from the argentaffin cells and postulated that the