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SOME EFFECTS OF 400 MEV PROTONS ON PRIMATES

The Radiations of Space IV

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FOREWORD

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The experiments reported herein were conducted according to the "Principles of Laboratory Animal Care" established by the National Society for Medical Research.

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This report has been reviewed and is approved.

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ABSTRACT

Primates were given spaced doses of 400 Mev protons. From the mortality data an $LD_{50/30}$ of 585 ± 33 (S.E.) rads was calculated. Hematologic measurements, LDH and SGOT concentrations, ^{59}Fe ferrokinetics, and histopathologic findings indicate the effects produced by the protons are virtually identical to those produced by equivalent doses of 2 Mev x-rays. The only differences in response were clinical; relatively more intense gastrointestinal and hemorrhagic signs occurred after proton irradiation than after similar doses of the x-rays.

SOME EFFECTS OF 400 MEV PROTONS ON PRIMATES

The Radiations of Space IV

I. INTRODUCTION

In previous studies the biologic effects of 32, 55, and 138 Mev protons have been examined (1, 2, 3). At these energies the predominant mode of energy deposition results from direct ionization; nuclear processes which produce high LET–high RBE particles (recoil nuclei, evaporation nucleons, and others) provide less than 10% of the total rad dose (4).

In the experiments described in this communication, the biologic effects produced by 400 Mev protons are explored. This energy is of interest because it is about the highest energy represented by significant numbers of protons in the space proton spectrum (5). Since at 400 Mev some 25% of the total rad dose results from nuclear processes (4), the use of a monoenergetic source of these protons allows an evaluation of biologic effects occurring when the relative concentration of the high LET–high RBE particles equals or exceeds the maximum anticipated from irradiation with the space proton spectrum.

II. EXPERIMENTAL METHODS AND MATERIALS

One hundred twenty-three small primates *(Macaca mulatta)* were used. Of these, there were 57 males and 66 females. They had a mean weight of 3.7 ± .6 (S.D.) kg. The animal care practices used at the USAF School of Aerospace Medicine have already been described (6).

The University of Chicago Cyclotron Facility was used as a source of the protons. The details of the experimental arrangement, the beam characteristics, and the dosimetry have been previously documented (7, 8). In all, 9 groups of 3 to 17 animals were given spaced single doses of protons ranging in size from 25 to 1,200 rads (table I). The protons were delivered at a dose rate of 16 rads/min.

From 7 of the dose groups (table I), selected animals were bled by femoral venipuncture before irradiation and at 1, 2, 4, 7, 15, 30, 60, and 90 days postexposure for hematologic studies and serum enzyme assays (6). Total white cell counts, white cell differentials, platelet counts, hemoglobin concentrations, microhematocrits, lactic dehydrogenase (LDH) concentrations, and glutamic oxalacetic transaminase (SGOT) concentrations were measured.

Five groups of 3 animals each were given doses of 25, 50, 100, 200, and 400 rads, respectively (tables I and IX). At least a month prior to irradiation, ^{59}Fe ferrokinetics were performed according to methods described by Lajtha (9); plasma disappearance half-times and 10-day RBC uptakes were measured. At 48 hours after exposure, the examinations were repeated.

A Van de Graaff accelerator was used for the 2 Mev x-irradiations. The experimental arrangement, the beam characteristics, and the dosimetry have already been described (6). A dose rate of 15 rads/min. was used. Five groups of 3 animals each received single doses of 25, 50, 100, 200, and 400 rads, respectively. Two sham-irradiated controls were also carried with this group. At least a month before exposure and at 48 hours postirradiation, ^{59}Fe ferrokinetics were performed.

During the first 60 postirradiation days, the animals were observed hourly for clinical changes and dead animals. They have been followed at about 8-hour intervals since the 60th day. All dead animals were necropsied and tissues processed according to methods already described (6).

TABLE I

Mortality after 400 Mev proton irradiation

Dose (rads)	Study	Number of animals	Number dead at 30 days (all groups)	Percent dead at 30 days	Mean survival time of nonsurvivors (days)
1,200	I. a. Bled				
	b. Nonbled	5	5	100	9
1,000	I. a. Bled*	4	10	100	9.9
	b. Nonbled	6			
800	I. a. Bled	4			—
	b. Nonbled	10	12	85.7	14
600	I. a. Bled	4	8	57	15.4
	b. Nonbled	10			—
400	I. a. Bled	4			—
	b. Nonbled	10	1	6	23
	II. †	3			—
200	I. a. Bled	4	0	0	—
	b. Nonbled	10			—
	II.	3			—
100	I. a. Bled	4			—
	b. Nonbled	10	0	0	—
	II.	3			—
50	I. a. Bled	4	0	0	—
	II.	3	0	0	—
25	II.	3			—

*Bled for hematologic studies and serum enzyme assays.

†^{59}Fe ferrokinetics.

III. RESULTS

The mortality results are summarized in table I, figure 1, and figure 2. From the cumulative mortality data, an $LD_{50/30}$ of 585 ± 33 (S.E.) rads was calculated by probit analyses (10). The equation for the regression is:

$$Y = 5.3075 + 9.2385\ (X-2.7994)$$

where Y is in probits and X in units of $\log_{10}$ of the doses. The chi-square for the regression is .2244 (3 d.f.), which is not significant and indicates no departure from linearity. The slope standard error is 1.7618.

Also plotted for figure 2 are results from a previous study in which primates were irradiated with 2 Mev x-rays (6). Notice that relatively little difference in the mortality patterns occurred, except for perhaps a minimal increase in early deaths after proton irradiation as compared with similar doses of x-rays.

Since the clinical changes which appeared after irradiation are virtually identical to those described following exposure to electromagnetic radiations and 138 Mev protons (3, 6, 11, 12, 13), only the more significant points will be considered. Doses of 800 rads and above produced severe gastrointestinal signs between the

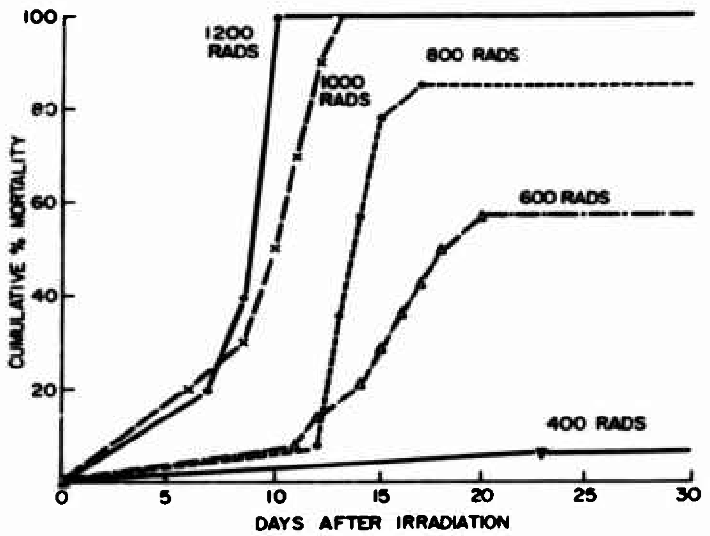

FIGURE 1

Cumulative mortality after irradiation. Since no deaths occurred after 200 rads and less, this was not plotted.

3d and 10th postirradiation days; mucous and bloody diarrhea were common. Lower doses (400 to 600 rads) caused proportionately less severe signs as compared with the higher doses. The gastrointestinal signs abated, however, in those animals which survived past the 10th day. This respite was only transitory, however, because evidence of hemorrhagic diatheses appeared on or about the 12th day. Extensive dermal petechiae and hemorrhages, gingival hematomas, and hemorrhages throughout the viscera were the most significant findings. Comparison of the clinical changes after 400 Mev proton irradiation with the findings from a previous study in which 2 Mev x-rays were used indicates a moderate increase in severity of both gastrointestinal disease and hemorrhage after equivalent doses of the protons (6).

The total white cell counts, the lymphocyte counts, the neutrophil counts, the platelet counts, the hemoglobin concentrations, and the hematocrits are summarized in tables II-VI, respectively. Both qualitatively and quantitatively, the changes of all of the measurements were similar to those previously observed in primates after orthovoltage and supervoltage electromagnetic radiations and after 138 Mev protons

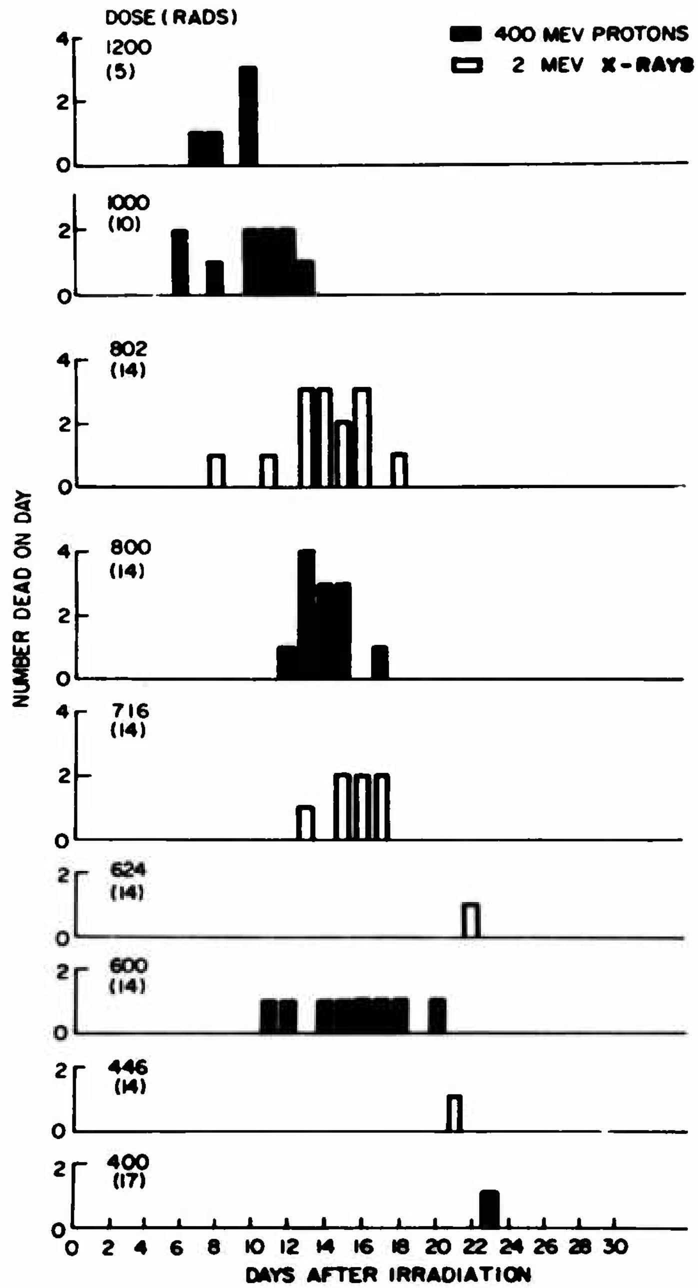

FIGURE 2

Daily mortality after irradiation with 400 Mev protons and 2 Mev x-rays.

(3, 6, 11, 13). During the first 2 postirradiation weeks, there occurred a progressive depression of the total white cell and lymphocyte counts—the latter, to a greater degree; a minimum was reached on day 15. The platelet counts remained at normal levels until the 15th

TABLE II

Total white cell count

	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	12,138	14,433	9,600	5,933	9,116	7,766	8,350	10,850	9,338
50 rads	11,612	6,475	6,650	7,462	7,725	5,600	7,888	9,250	9,700
100 rads	10,588	4,500	2,787	3,800	3,900	5,075	4,925	7,663	9,525
200 rads	10,612	5,450	3,188	3,112	3,750	3,075	4,450	9,688	11,063
400 rads	9,725	4,250	2,212	2,125	1,412	975	5,613	5,625	9,975
600 rads									
A	9,850	5,488	1,525	2,275	2,150	750	12,666	14,066	10,617
S	5,513	5,733	1,433	2,033	2,550	933	12,666	14,066	10,617
N-S*	12,600	4,750	1,800	3,000	950	200	—	—	—
800 rads									
A	11,550	7,188	4,050	2,437	1,425	400	4,500	11,300	6,500
S*	14,300	9,700	7,500	2,700	1,650	450	4,500	11,300	6,500
N-S	10,633	6,350	2,900	2,350	1,350	350*	—	—	—
1,000 rads (all N-S)	10,500	8,288	3,137	1,725	2,900	—	—	—	—

The entries in the table are the average counts, per cubic millimeter, of 4 bled animals (except the survivor and nonsurvivor subdivisions of the 600- and 800-rad groups).

A = All animals. S = Survivors. N-S = Nonsurvivors.

*One animal.

TABLE III

Lymphocytes

	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	8,168	6,117	6,300	2,838	6,264	5,033	6,153	9,017	7,289
50 rads	8,459	3,130	3,090	3,214	5,382	3,364	5,693	7,496	7,785
100 rads	6,412	2,714	1,579	1,717	2,027	3,639	2,399	4,051	6,951
200 rads	5,025	1,686	999	779	1,698	2,407	3,189	5,963	6,929
400 rads	6,880	1,072	610	438	710	707	4,213	3,013	6,636
600 rads									
A	6,219	1,176	422	852	1,254	663	8,073	8,812	8,052
S	5,268	1,283	383	735	1,520	840	8,073	8,812	8,052
N-S*	9,072	855	540	1,200	456	130	—	—	—
800 rads									
A	8,901	1,534	870	609	977	264	2,475	6,554	2,665
S*	10,868	2,716	1,275	432	858	275	2,475	6,554	2,665
N-S	8,246	1,140	735	668	1,017	252*	—	—	—
1,000 rads (all N-S)	7,206	1,479	473	506	1,418	—	—	—	—

The entries in the table are the average counts, per cubic millimeter, of 4 bled animals (except the survivor and nonsurvivor subdivisions of the 600- and 800-rad groups).

A = All animals. S = Survivors. N-S = Nonsurvivors.

*One animal.

TABLE IV

Neutrophils

	Baseline	Days after irradiation								
		1	2	4	7	15	30	60	90
Controls	3,679	8,199	3,193	3,008	2,766	2,504	2,014	1,550	1,432
50 rads	2,957	3,169	3,483	4,155	2,294	2,140	2,084	1,683	1,433
100 rads	3,780	1,700	[illegible]101	1,999	1,815	1,330	1,958	3,523	2,139
200 rads	5,408	3,627	2,048	2,314	2,028	650	936	3,515	3,248
400 rads	2,700	3,131	1,527	1,669	696	242	1,251	2,460	3,060
600 rads									
A	3,328	4,255	1,052	1,372	891	82	3,979	4,000	1,790
S	3,346	4,375	1,019	1,249	1,030	86	3,979	4,000	1,790
N-S*	3,276	3,895	1,152	1,740	475	70	—	—	—
800 rads									
A	2,184	5,592	3,123	1,813	432	127	1,845	4,294	3,445
S*	2,717	6,984	6,225	2,268	729	162	1,845	4,294	3,445
N-S	2,007	5,128	2,089	1,661	333	91*	—	—	—
1,000 rads									
(all N-S)	2,911	6,749	2,626	1,202	563	—	—	—	—

The entries in the table are the average counts, per cubic millimeter, of 4 bled animals (except the survivor and nonsurvivor subdivisions of the 600- and 800-rad groups).

A = All animals. S = Survivors. N-S = Nonsurvivors.

*One animal.

TABLE V

Platelets

	Baseline	Days after irradiation								
		1	2	4	7	15	30	60	90
Controls	246	305	297	287	258	262	286	272	331
50 rads	370	270	203	243	279	263	256	261	321
100 rads	372	350	326	372	310	212	249	249	302
200 rads	353	308	265	366	340	151	304	231	260
400 rads	402	322	282	327	248	91	232	238	285
600 rads									
A	340	351	332	317	181	81	186	286	305
S	348	336	326	328	171	105	186	286	305
N-S*	316	394	351	286	212	9	—	—	—
800 rads									
A	356	290	312	325	149	8	138	274	394
S*	334	269	278	321	139	4			
N-S*	363	297	324	326	152	12*	—	—	—
1,000 rads									
(all N-S)	327	329	377	328	142	—	—	—	—

The entries in the table are the average counts ($\times 10^3/mm.^3$) of 4 bled animals (except the survivor and nonsurvivor subdivisions of the 600- and 800-rad groups).

A = All animals. S = Survivors. N-S = Nonsurvivors.

*One animal.

TABLE VI

Hemoglobin (gm./100 ml. blood) and hematocrit (%)

	Baseline		Days after irradiation																	
			1		2		4		7		15		30		60		90	
	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT
Controls	11.2	37	12.6	40	11.6	37	10.9	35	10.5	33	10.0	32	10.1	33	11.5	36	11.6	37
50 rads	12.4	40	11.7	37	12.6	38	12.3	39	10.6	34	10.0	33	12.6	40	12.2	38	12.6	39
100 rads	12.4	40	12.4	40	11.2	36	11.0	35	10.8	34	10.3	33	11.4	36	12.2	38	12.5	40
200 rads	12.5	42	11.9	38	11.1	36	10.8	35	10.5	34	9.9	32	10.3	33	12.3	39	12.0	39
400 rads	13.3	42	12.4	40	12.1	39	11.4	37	10.7	34	9.1	30	9.6	31	13.1	42	13.0	41
600 rads																		
A	11.7	38	12.0	38	11.5	37	10.9	36	10.0	34	6.4	22	9.0	30	11.5	38	11.9	38
S	11.2	36	11.9	38	11.2	36	10.8	36	10.2	34	7.2	25	9.0	30	11.5	38	11.9	38
N-S*	13.1	41	12.4	38	12.2	39	11.1	35	9.7	33	4.0	15	—	—	—	—	—	—
800 rads																		
A	12.3	39	12.0	39	11.6	37	11.6	37	11.4	36	6.4	22	9.2	31	11.4	35	14.5	46
S*	14.1	43	12.4	40	11.5	35	10.8	35	10.6	34	7.7	27	9.2	31	11.4	35	14.5	46
N-S	11.6	38	11.8	38	11.7	38	11.8	37	11.7	36	5.0*	18*	—	—	—	—	—	—
1,000 rads (all N-S)	12.1	39	11.4	37	11.4	38	11.4	36	11.8	34	—	—	—	—	—	—	—	—

The entries in the table are the average measurements of 4 bled animals (except the survivor and nonsurvivor subdivisions of the 600- and 800-rad groups).

A = All animals. S = Survivors. N-S = Nonsurvivors.

*One animal.

day when a severe depression appeared in those animals which had beer given doses of 400 rads or greater.

A similar pattern was observed for the hemoglobin-hematocrit levels. After doses of 400 rads or less, relatively minor changes of the measurements were found during the postirradiation period, except for a minimal drop during the first few days, which seems to be a consequence of the frequent sampling and not due to actual changes in the hematopoietic mechanism (6). Doses above 400 rads produced a moderate depression of the hemoglobin-hematocrit levels on the 15th day; progressive improvement followed, however, in the survivors.

The LDH and SGOT concentrations are summarized in tables VII and VIII, respectively. The changes in the concentrations of these enzymes are very similar to those found in the primate after 2 Mev x-rays and 138 Mev proton irradiation (3, 6). While doses of 50 rads of 400 Mev protons produced a significant elevation (by Student's t-test) of the LDH level above the normal range on days 7 and 15, doses of 200 rads or more were required to produce consistent elevations of both enzyme levels during the first 4 postirradiation days; normal ranges, however, were reached by the 7th day.

The results of the ^{59}Fe measurements are given in table IX. For this experiment, equal doses of 2 Mev x-rays and 400 Mev protons delivered at approximately the same dose rates were given to groups of monkeys. Doses of 100 rads or more of either quality of radiation caused significant prolongation of the plasma disappearance half-times and depression of the 10-day RBC uptake. While doses of 25 and 50 rads did not produce changes which could be detected by Student's t-test, numeric prolongation of the plasma disappearance half-times and depression of the RBC uptakes beyond preirradiation baseline values occurred after these doses. When the responses produced by a given dose level of 400 Mev protons were compared with the responses after the 2 Mev x-rays, no significant differences were found.

TABLE VII

Lactic dehydrogenase (LDH)

	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	518 ± 33†	413 ± 41	476 ± 56	430 ± 81	595 ± 137	497 ± 55	732 ± 200¶	413 ± 119	500 ± 91
50 rads	580 ± 34	643 ± 290	419 ± 27	588 ± 151	807 ± 129‡	823 ± 150‡	417 ± 106	385 ± 45	466 ± 51
100 rads	566 ± 78	585 ± 112	439 ± 174	497 ± 56	577 ± 75	558 ± 85	465 ± 46	380 ± 110	480 ± 193
200 rads	605 ± 113	896 ± 163‡	825 ± 398‡	676 ± 154	598 ± 142	400 ± 86	542 ± 132	469 ± 68	424 ± 64
400 rads	586 ± 110	1,003 ± 326‡	744 ± 223¶	715 ± 187	509 ± 52	417 ± 107	642 ± 180	355 ± 92	400 ± 83
600 rads									
A	593 ± 82	1,355 ± 212‡§	1,096 ± 410‡	759 ± 308¶	547 ± 91	496 ± 70	644 ± 112	458 ± 39	450 ± 138
S	610 ± 87	1,443 ± 174	1,135 ± 460	817 ± 333	569 ± 96	462 ± 44	644 ± 112	458 ± 39	450 ± 138
N-S*	543	1,090	977	583	480	600	—	—	—
800 rads									
A	546 ± 119	1,293 ± 349‡‖	1,210 ± 163‡§	905 ± 284‡	483 ± 140	755	426	[illegible]	646
S*	556	1,790	1,376	763	396	430	426	346	646
N-S	543 ± 118	1,128 ± 107	1,154 ± 116	953 ± 311	512 ± 152	1,080*	—	—	—
1,000 rads (all N-S)	528 ± 89	1,323 ± 251‡§	1,350 ± 270‡§	1,164 ± 316‡‖	611	—	—	—	—

The entries in the table are the means and standard deviations, in units per milliliter of serum, of the measurements of 4 bled animals (except the survivor and nonsurvivor subdivisions of the 600- and 800-rad groups). Where no standard deviation is listed, less than three measurements were available.

Normal range based on 198 normal examinations, 540 ± 146 units.

A = All animals. S = Survivors. N-S = Nonsurvivors.

*One animal.

†Standard deviation.

‡P < .001 compared with pre-established normal range.

§P < .001 compared with preirradiation baseline.

‖P < .01 compared with preirradiation baseline.

¶P < .01 compared with pre-established normal range.

TABLE VIII

Glutamic oxalacetic transaminase (SGOT)

	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	33 ± 3†	27 ± 1	42 ± 19	36 ± 1	31 ± 6	28 ± 5	28 ± 4	28 ± 5	26 ± 4
50 rads	30 ± 7	34 ± 5	26 ± 5	34 ± 6	33 ± 7	30 ± 3	22 ± 2	22 ± 2	25 ± 3
100 rads	31 ± 2	32 ± 6	30 ± 5	34 ± 5	39 ± 12‖	27 ± 1	23 ± 3	24 ± 4	28 ± 10
200 rads	29 ± 2	45 ± 16‡	46 ± 21‡	40 ± 7‖	33 ± 6	24 ± 3	23 ± 6	25 ± 6	22 ± 3
400 rads	35 ± 8	68 ± 62‡	42 ± 30‖	33 ± 10	34 ± 5	26 ± 3	24 ± 2	23 ± 3	24 ± 2
600 rads									
A	28 ± 8	65 ± 17§	32 ± 8	29 ± 7	29 ± 9	28 ± 14	24 ± 6	30 ± 6	26 ± 2
S	27 ± 8	71 ± 16	34 ± 9	30 ± 7	30 ± 10	20 ± 5	24 ± 6	30 ± 6	26 ± 2
N-S*	32	49	27	26	25	50	—	—	—
800 rads									
A	30 ± 2	98 ± 65‡	80 ± 44‡	64 ± 44‡	24 ± 5	45	22	22	26
S*	28	211	150	52	25	18	22	22	26
N-S	31 ± 0	61 ± 6	56 ± 21	67 ± 50	23 ± 6	71*	—	—	—
1,000 rads (all N-S)	31 ± 4	127 ± 72‡	135 ± 88‡	71 ± 45‡	33	—	—	—	—

The entries in the table are the means and standard deviation, in units per milliliter of serum, of the measurements of 4 bled animals (except the survivor and nonsurvivor subdivisions of the 600- and 800-rad groups). Where no standard deviation is listed, less than three measurements were available.

Normal range based on 198 normal examinations, 31 ± 6 units.

A = All animals. S = Survivors. N-S = Nonsurvivors.

*One animal.

†Standard deviation.

‡$P < .001$ compared with pre-established normal range.

§$P < .01$ compared with preirradiation baseline.

‖$P < .01$ compared with pre-established normal range.

TABLE IX

^{59}Fe ferrokinetics after 2 Mev x- and 400 Mev proton irradiation

Dose (rads)	Plasma disappearance half-time (min.)				10-day RBC uptake (% of injected dose)			
	400 Mev protons		2 Mev x-rays		400 Mev protons		2 Mev x-rays	
	Before irr.	After irr.	Before irr.	After irr.	Before irr.	After irr.	Before irr.	After irr.
0 (sham-irradiated)	—	—	55	88	—	—	98	75
25	85 ± 19	116 ± 18	8[illegible] ± 13	10[illegible] ± 12	89 ± 4	87 ± 18	90 ± 13	75 ± 6
50	74 ± 26	111 ± 21	85 ± 9	163 ± 17†	87 ± 11	92 ± 14	97 ± 4	61 ± 6
100	86 ± 23	221 ± 62*	82 ± 16	176 ± 38‡	93 ± 7	56 ± 20*	84 ± 5	53 ± 15
200	70 ± 14	211 ± 11†	81 ± 23	215 ± 14†	88 ± 12	34 ± 16‡	88 ± 11	18 ± 14†
400	65 ± 22	335 ± 89‡	94 ± 14	267 ± 34†	95 ± 9	0 ± 0†	88 ± 5	2.2 ± 4†

The entries in the table are the means and standard deviations of the measurements from 3 animals, except for the sham-irradiated controls where there were 2 animals.

*$P < .05$ compared with preirradiation baseline.

†$P < .001$ compared with preirradiation baseline.

‡$P < .01$ compared with preirradiation baseline.

Since the histopathologic examination of the tissues taken at necropsy showed changes which were very similar to those found after 2 Mev x-ray and 138 Mev proton irradiation (3, 6), only a brief description of the findings will be given. A detailed analysis of the tissue changes after 400 Mev proton irradiation will be published separately. There were prominent changes throughout the large and small intestine; these changes included denudation of the mucosa and extensive microhemorrhages. While these findings were present in all dead animals, they were more severe in the higher dose groups (800 to 1,200 rads). All dead animals had aplasia of the bone marrow and severe hypoplasia of the lymph follicles of the spleen and lymph nodes. As was seen after 2 Mev x-irradiation, there were bacterial colonies scattered throughout the liver, lungs, kidneys, lymph nodes, and skin (6). Also, the lungs of several animals had the small abscesses without leukocytic infiltration as previously found in 2 Mev x-irradiated animals. When the tissue of animals which received equivalent doses of 2 Mev x-rays and 400 protons were compared, no significant differences were found.

IV. DISCUSSION

In an earlier study a large group of primates were irradiated with 2 Mev x-rays (6); these results will serve as an electromagnetic standard for estimating the relative biologic effectiveness (RBE) of the 400 Mev protons. As previously described, a most important consideration, in the estimation of RBE's by comparison of the $LD_{50/30}$'s, concerns parallelism of the probit regression curves (3, 10. 17). As Finney has stated, there are serious theoretic difficulties associated with estimating the relative potencies (RBE's in this case) of 2 or more treatments (radiations) when the probit regression curves are not parallel. A chi-square of 1.0185 (1 d.f.) for deviation from parallelism between the regression curves for 2 Mev x-rays and 400 Mev protons was calculated according to Finney's method (10). Since this value is not significant at the .05 level, the possibility of a significant departure from parallelism is rejected.

Because there is no reason to suspect deviation from parallelism, the RBE may be determined by the ratio of the $LD_{50/30}$'s. The $LD_{50/30}$ produced by 2 Mev x-rays was 670 $\pm$ 21 (S.E.) rads, and the $LD_{50/30}$ found after 400 Mev proton irradiation was 585 $\pm$ 33 (S.E.) rads; from these results, an RBE of 1.14 $\pm$ .07 (S.E.) was estimated (6).

Another important consideration is that of dose rate. Since many biologic effects produced by electromagnetic radiations are affected by the rate of delivery of the doses (14, 15, 16), this factor may play an important role in the present situation. Although the mortality after proton irradiation has not yet been shown to be dose-rate dependent, fragmentary evidence exists which suggests that such may be the case (17). To compensate for the possible influence of dose rate, the 2 Mev x-ray $LD_{50/30}$ was adjusted to the proton dose rate by a mathematical model derived by Bateman et al. (16). After this alteration had been made, an adjusted RBE of 1.09 was calculated. It is evident, therefore, that the 400 Mev proton–2 Mev x-ray RBE for mortality is essentially unity.

The prominent gastrointestinal signs after proton irradiation have been observed in both primates and rodents (3, 17, 18, 19). In the previous study in which 138 Mev protons were used, the gastrointestinal signs were somewhat more severe than in the present case. Since the 138 Mev protons were delivered at 57 rads/min. while the 400 Mev protons were given at 16 rads/min., part or all of this difference may be a consequence of the variation in dose rate. Comparison of the clinical findings after 2 Mev x-rays with both the 138 and 400 Mev proton experience, however, shows unequivocally that more severe signs were produced by the protons. Unfortunately, no explanation for this finding is available at present.

A similar circumstance exists about the severity of the postirradiation hemorrhagic disease. After both 138 and 400 Mev proton exposure, the degree of hemorrhage was considerably more extensive than after 2 Mev x-irradiation. Where small dermal petechiae appeared after the x-rays, equivalent doses of the protons produced massive intradermal hemorrhages. Attempts to explain this phenomenon on physical grounds alone have been unsuccessful (3). There seems to be relatively little (if any) buildup of dose in the bone marrow cavities after the proton irradiation as compared to the x-rays.

A possible mechanism may be found in the clinical experience of physicians treating patients with chronic thrombocytopenia. In these cases a minimal infection or a transient bacteremia seems to trigger a hemorrhagic crisis (20-23). Since there appears to be considerably more gastrointestinal injury after the proton exposures, the injured intestinal epithelium could conceivably allow intermittent showers of bacteria into the bloodstream and increase the severity of the thrombccytopenia. Since no blood samples were taken on days 8 to 14 or 16 to 29, the failure to find a sharply lowered platelet count is possible, especially if the hemorrhage episodes occurred as fulminant crisis and produced death in a matter of hours. Because the gastrointestinal signs after 2 Mev x-irradiation are considerably less severe than after proton exposure, it is possible that such bacteremias would be less likely to occur if the degree of intestinal injury was proportionately less severe. There are findings, however, which do not directly support the hypothesis just given. Although the histologic sections of the intestines after both protons and the x-rays show extensive changes, no real differences in response can be quantitated. Therefore, the possibility that the increased hemorrhage

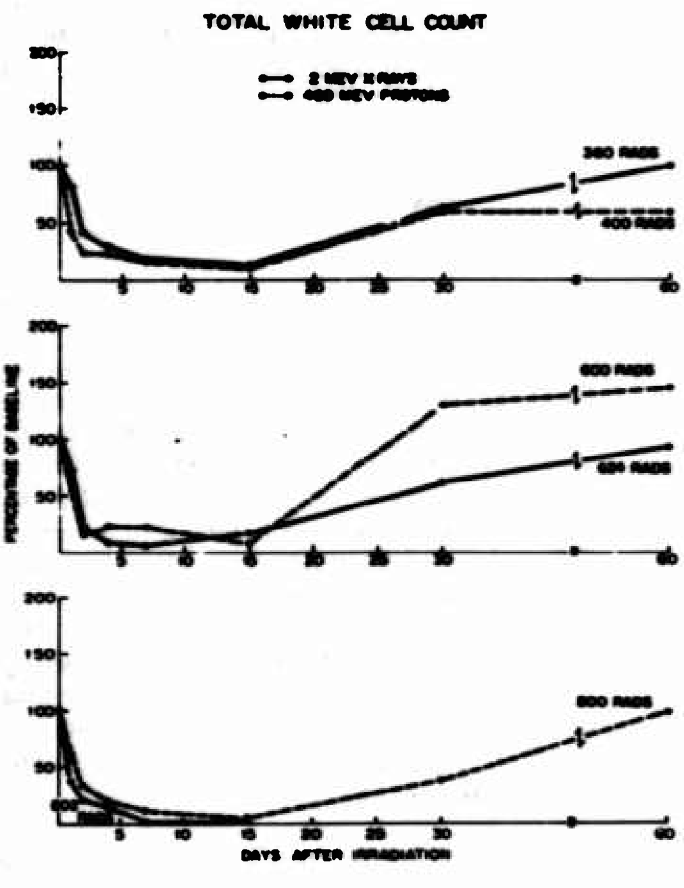

FIGURE 3

Total white cell counts after 400 Mev protons and 2 Mev x-rays. There were no survivors past 15 days after 802 rads of Mev x-rays.

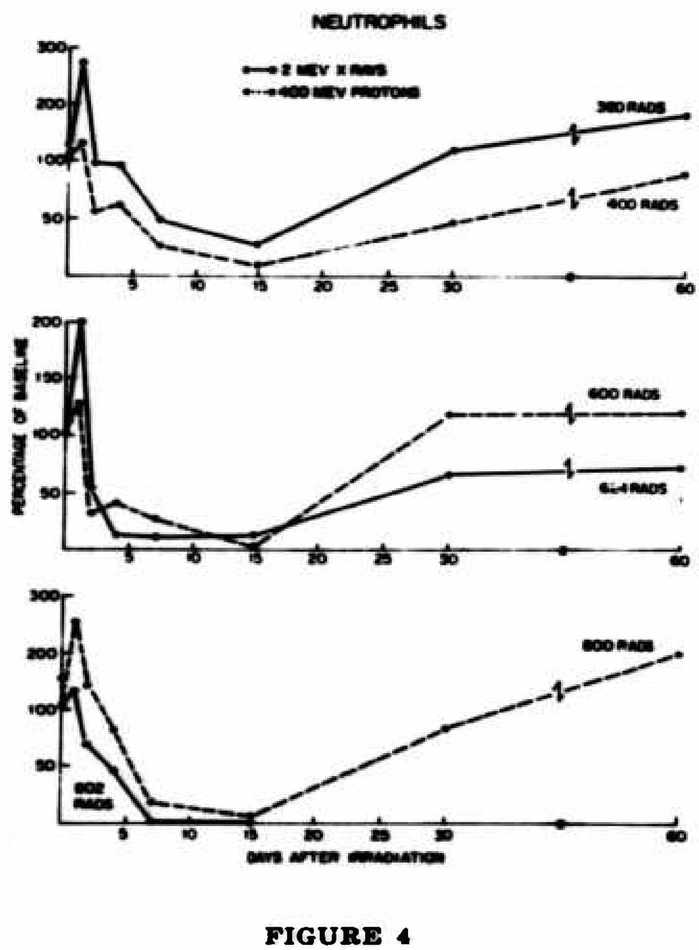

FIGURE 4

Neutrophil counts after 400 Mev protons and 2 Mev x-rays.

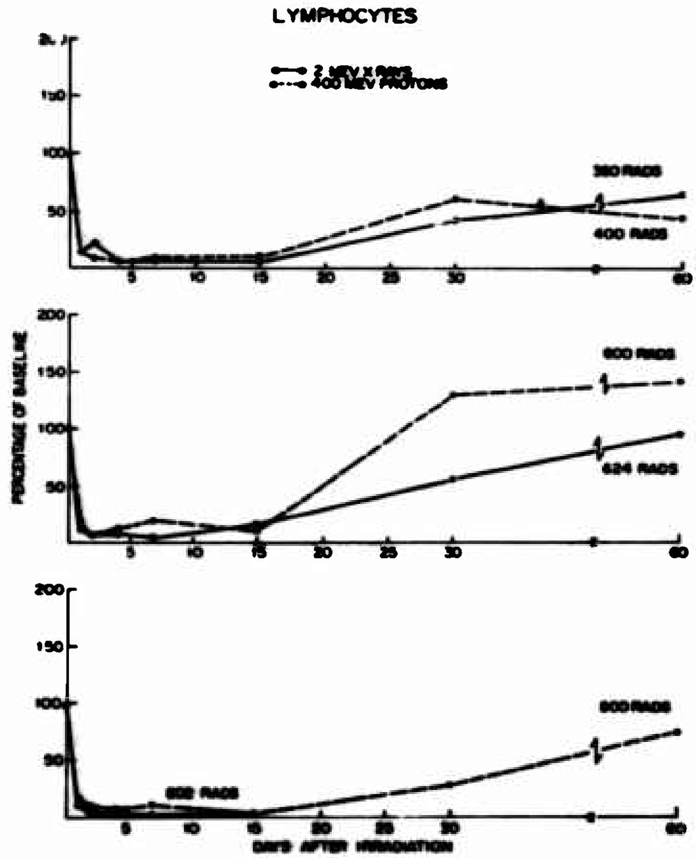

FIGURE 5

Lymphocyte counts after 400 Mev protons and 2 Mev x-rays.

may be due to an increased incidence in infection after the protons is highly speculative, and further studies are certainly indicated.

Although doses of 100 rads did not produce any detectable clinical findings, there is bone marrow injury, as indicated by the ^{59}Fe ferrokinetics and the white cell counts. No clinical evidence of hemorrhage occurred until doses of 200 rads of either 400 Mev protons or the 2 Mev x-rays were given. With increasing doses above 400 rads of the 400 Mev protons, there is proportionately more evidence of biologic injury as indicated by the ^{59}Fe ferrokinetics, the blood counts, and the serum enzyme levels.

Doses of 780 rads of 138 Mev protons and 800 rads of 400 Mev protons seem to be about

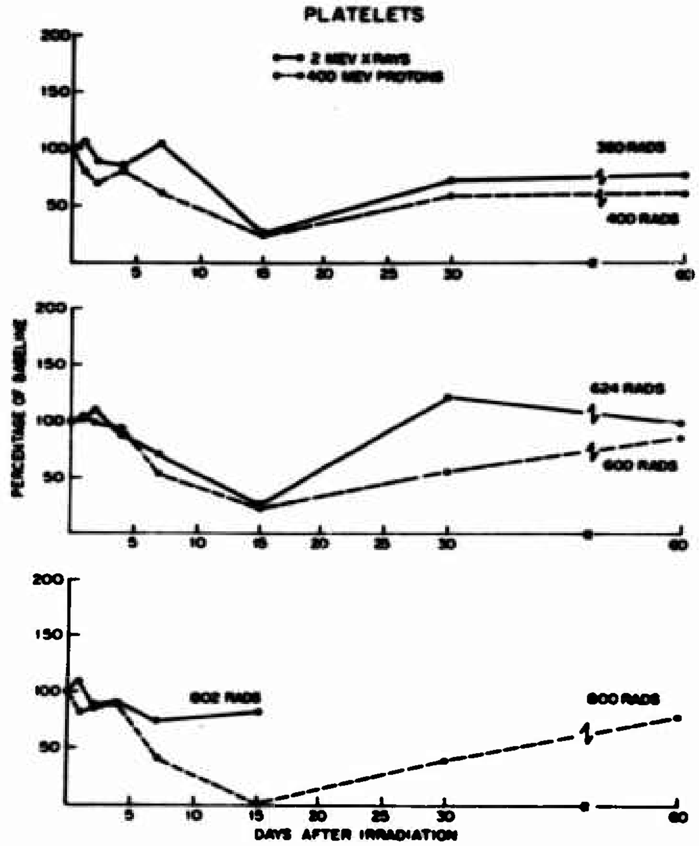

FIGURE 6

Platelet counts after 400 Mev protons and 2 Mev x-rays. The somewhat unexpected high platelet count after 802 rads of 2 Mev x-rays occurred in a single animal in terminal status and severely dehydrated. Our impression is that the dehydration caused hemoconcentration, which produced a platelet count that was excessively high.

the level at which deaths from the "gastrointestinal syndrome" appear. These animals die before the 12th postirradiation day with relatively normal platelet counts and without clinical evidence of increased bleeding tendency. When responses of equivalent doses of supervoltage electromagnetic radiations are compared with these protons, an additional 100 rads of the electromagnetic radiations above the proton doses are necessary to produce the same degree of gastrointestinal signs.

For the determination of the rad doses, the calculations published earlier were used (4, 7, 8); these values are based on Monte Carlo an-

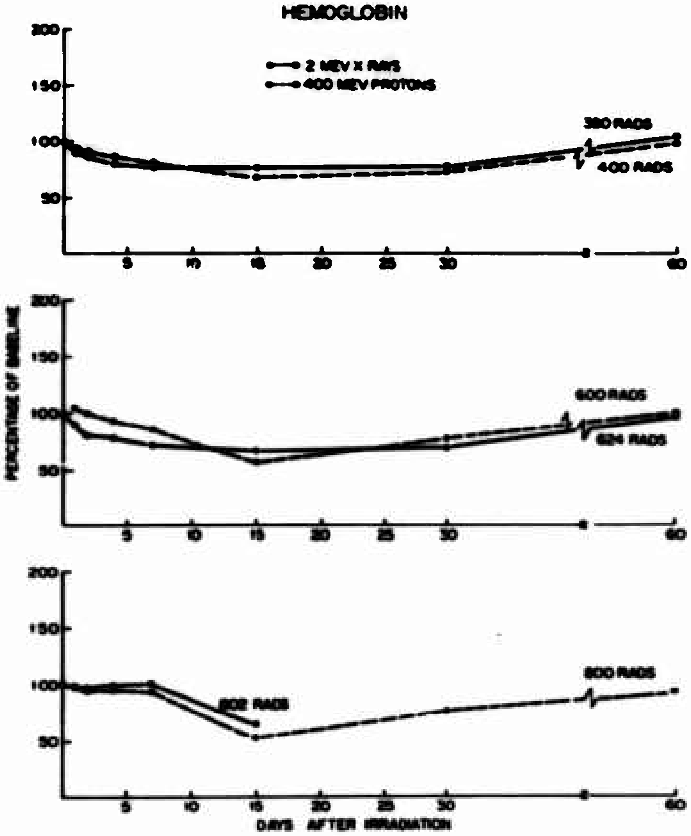

FIGURE 7

Hemoglobin concentrations after 400 Mev protons and 2 Mev x-rays.

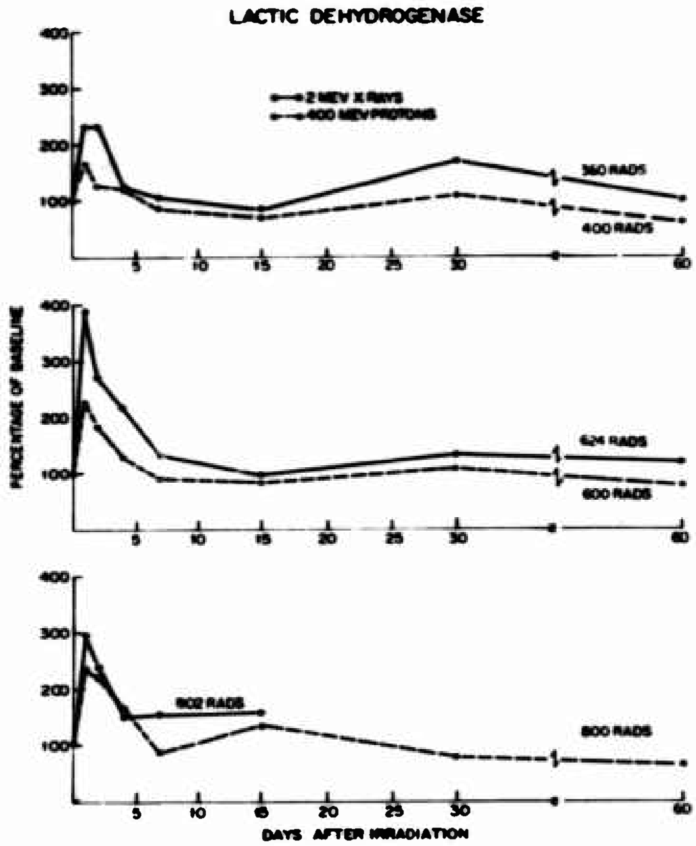

FIGURE 8

Serum lactic dehydrogenase (LDH) concentrations after 400 Mev protons and 2 Mev x-rays.

alyses, which consider a wide variety of nuclear processes in addition to primary ionization. Therefore, the rad doses based on these data include contributions from both ionization and the nuclear processes. When biologic responses after equivalent doses of 400 Mev protons are compared with effects produced by 2 Mev x-rays, nò real differences are found, except for relatively minor differences in clinical courses. This similarity is emphasized by figures 3-8. In these figures the response of the total white cell counts, the neutrophil counts, the lymphocyte counts, the platelet counts, the hemoglobin concentration, and the LDH concentrations after 400 Mev protons is compared with results produced by equivalent doses of the 2 Mev x-irradiations. The similarity of responses indicates that the RBE is unity for changes in these measurements. The ^{59}Fe ferrokinetics given in table IX also emphasize this point. Therefore, we have no evidence to suggest that the response to 400 Mev protons differs significantly from the response to 2 Mev x-rays.

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Primates were given spaced doses of 400 Mev protons. From the mortality data an $LD_{50/30}$ of 585 ± 33 (S.E.) rads was calculated. Hematologic measurements, LDH and SGOT concentrations, ^{59}Fe ferrokinetics, and histopathologic findings indicate the effects produced by the protons are virtually identical to those produced by equivalent doses of 2 Mev x-rays. The only differences in response were clinical; relatively more intense gastrointestinal and hemorrhagic signs occurred after proton irradiation than after similar doses of the x-rays.

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