

Failure of Folic Acid to Influence Lethal Radiation Illness in Swine.* (17724)

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Following the synthesis of folic acid by Angier *et al.*(1), there were many reports on its beneficial effects in the therapy of pernicious anemia, sprue, nutritional macrocytic anemia and nutritional granulopenias of animals(2,3,4). Watson *et al.*(5), reported that folic acid might be of value in the therapy of refractory anemias and leukopenias, particularly the leukopenia following radiation therapy. This suggested that folic acid might be of value in the therapy of the pancytopenia that follows total body exposure to ionizing radiation. An experiment to investigate the effect of folic acid on the blood picture and lethality of total body exposure to x-ray was performed.

Methods. Eight adult swine(200 ± 50 lb) were given 400 r total body exposure to 1000 kv x-rays according to the method previously described(6). Folic acid was administered intramuscularly in doses of 45 mg per day to 4 of the 8 swine beginning the day after exposure and continuing until the death of the animal. The clinical course, the blood

picture, sternal marrow, and post mortem pathological findings were recorded.

Results. The mortality was 100% in both the control untreated swine and in the folic acid-treated swine. The average survival time of the treated swine was 14.7 days as compared with 14.2 days for the control untreated swine. The treated swine died between the 13th and 17th days and the untreated swine between the 12th and 16th days after exposure. The clinical course of both groups was similar. Scattered petechiae were visible on the second and third days after exposure. Hemorrhagic phenomena were prominent from the 10th day after exposure until death in all animals. One of the treated animals developed an abscess at the point of injection which was incised on the third day after exposure. Cultures were positive for *Hemophilus hemolyticus* and a diphtheroid. Although the pig died on the 13th day after exposure the abscess appeared to be healing despite the low white count.

In Table I are given the average group hematological values for both the control untreated and the treated swine. There is no significant difference between the two groups in respect to the differential cell count, or the various erythrocytic indices and mean values.

The gross and microscopic lesions in the control and test swine were similar in kind, distribution and in severity. It was not possible to distinguish by pathological examination between the treated and the untreated swine.

Comments. The mechanism by which folic acid acts in the therapy of macrocytic anemias is not clear. The role of folic acid in normal hematopoiesis is not well understood(4,7,8). How folic acid might ameliorate the severity of total body radiation illness would be difficult to understand in the light of our present knowledge. The reports of Watson *et al.*(5), and Davis(9) on the beneficial effect of folic

* The Folvite solution (sodium salt of folic acid) was supplied by courtesy of Dr. T. H. Jukes, Lederle Laboratories Division, American Cyanamid Co., Pearl River, N.Y.

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TABLE I.
Group Average Hematological Observations of Folic-Acid-Treated and Control Swine After Exposure to 400 r Total Body Irradiation

Hematological observations of treated and untreated swine		Control value	1	2	3	4	6	7	10	14	15	16
Total WBC	Treated	18.6	5.5	6.5	6.9	5.7	1.1	1.5	1.0	1.1	1.4	1.6
× 10 ³ /mm ³	Untreated	16.1	5.2	5.4	6.3	4.1	1.9	1.9	1.6	0.8	1.2	
Total lymphocytes	Treated	10.8	1.3	1.1	1.4	1.5	0.7	0.9	0.9	0.9	1.3	1.5
× 10 ³ /mm ³	Untreated	11.7	1.7	1.6	1.1	1.6	1.4	0.8	0.7	0.8		
Total neutrophils	Treated	7.6	4.1	5.3	5.5	4.1	0.4	0.6	0.1	0.2	0.1	0.1
× 10 ³ /mm ³	Untreated	5.3	3.4	3.7	5.1	2.5	0.5	1.1	0.9	0.1		
Total RBC	Treated	6.7			6.6		6.0	5.5		3.3		1.6
× 10 ⁶ /mm ³	Untreated	7.3			6.3		6.4	5.9		4.1		
Hemoglobin	Treated	13.8			13.9		12.4	11.1		6.3		
in g/100 cc	Untreated	13.8			14.0		13.3	13.2		8.5		
Hematocrit in %	Treated	42.			42.		38.	35.	35.	18.	13.	9.
	Untreated	44.			39.		39.	38.	38.	26.	12.	
Reticulocytes in %	Treated	2.0			0.3			0.2	0.9	1.4	1.2	0.7
	Untreated	2.0			0.3			0.3	0.2	0.3	3.2	
Platelets × 10 ³ per mm ³	Treated	160.			102.			45.	45.	15.		
	Untreated	130.			112.			68.	23.	10.		
Mean corpuscular volume	Treated	64.			60.		63.		64.	56.		56.
in μ ³	Untreated	60.			62.		61.		65.	65.		
Mean corpuscular hemo-	Treated	21.			21.		21.		20.	19.		
globin, μμg	Untreated	19.			22.		21.		22.	21.		
Mean corpuscular hemo-	Treated	31.			30.		30.		31.	29.		
globin conc. in %	Untreated	32.			28.		29.		29.	30.		

acid in fractional therapeutic irradiation cannot be compared with single dose total body radiation as described in the present paper or in the recent report of Adams(10) where folic acid was shown to be ineffective in the treatment of irradiation leukopenia in the cat. Goldfeder *et al.*(11) present data showing that there is no appreciable effect on the hematopoietic system of mice given pyridoxine or folic acid, but that there is a significant prolongation of the survival time of irradiated

mice receiving pyridoxine or folic acid. This later work is of great interest and should be confirmed on mice and other animals.

In the present study only 400 r of X-irradiation was used. This dose corresponds to approximately LD₈₅₋₉₀ for swine(6). It is possible that folic acid might be of benefit at other lethal doses. This possibility was not explored.

Summary and conclusions. 1. Eight swine were exposed to 400 r total body radiation. Four were treated with intramuscular injections of 45 mg of folic acid per day. The clinical and hematological courses were observed and postmortem examinations were performed. No differences were observed in the responses of the treated and untreated swine.

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