

served in the 3 week period and only 2 in the 4 week period. Allowing a period of at least 4 months for the control animals to develop tumors, it was found that 50% of the estrogen treated animals, 22% of the animals receiving Ethanol in sesame oil or no injections, and one, or 25% of the "proluton" treated animals showed tumor growth, to compare with the 85% tumor growth within 4 weeks with the test material.

One small series of intact mice with transplanted tumor, divided into "progesterone compound" treated, estrogen treated, "proluton" treated, and control groups of 3 animals each, was studied. These animals were also allowed to breed. Of this group only one, a progesterone compound treated mouse, developed a tumor.

Subsequent groups of animals with tumor transplants of the second and third generations, observed for only 6 weeks, are shown in Table II. These confirm the previous findings with 90% of the "compound" treated, 55% of the estrogen treated, and none of the "proluton" treated animals showing tumor

growth.

Additional facts in evaluating the action of the "progesterone compound" are: (1) 7 of the "progesterone compound" treated animals of the original 26 died of their tumors within the period 1 to 3½ months after transplantation, while none of the other animals of the original 3 series died of their tumors up to 4 months after transplantation. Many animals were sacrificed in all groups but in every instance the animals in the control groups were permitted to live longer because their tumors were smaller; (2) 2 of the "progesterone compound" treated animals developed gross and several had microscopic metastases, while no animals of the other groups showed metastatic spread.

More detailed studies are being carried out. One obvious line of investigation will be the effect of other hormones especially androgens on the growth of this tumor. It is always possible that this growth stimulation is due to some other material present in the "compound", which can be proven only by more detailed chemical work.

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Effects of Folic Acid on the Anemia Induced by X Irradiation.

S. PHYLLIS STEARNER. (Introduced by A. M. Brues.)

From the Biology Division of the Argonne National Laboratory, Chicago, Ill.

Previous work in this laboratory has shown that the anemia which followed radiations from internal and external sources was frequently macrocytic.^{1,2} The macrocytosis may have been the result of damage directly to the bone marrow or indirectly through damage to the viscera, resulting in failure to form an anti-anemia factor. Folic acid, classified as a vita-

min of the B complex, is reported to be similar in its action to liver extract. It has been shown to be effective therapeutically in certain of the macrocytic anemias in man.^{3,4} It was without effect, however, upon the macrocytic anemia that resulted from administration of Sr⁸⁹.^{5,6} Total-body X irradiation, unlike radioactive strontium, causes damage to the viscera as well as bone marrow. It is

¹ Stearner, S. P., Simmons, E. L., and Jacobson, L. O., to be published, 1948.

² Simmons, E. L., and Jacobson, L. O., Radio-toxicity of injected Sr⁸⁹ for rats, mice and rabbits. Part IV. The hematological effects of enterally and parenterally administered Sr⁸⁹ in mammals. National Nuclear Energy Series, Vol. 22b.

³ Spies, T. D., Vilter, R. W., Koch, M. B., and Caldwell, M. H., *Southern Med. J.*, 1945, **38**, 707.

⁴ Moore, C. V., Vilter, R. W., Manneck, V., and Spies, T. D., *J. Lab. and Clin. Med.*, 1944, **29**, 1226.

⁵ Jacobson, L. O., Stearner, S. P., and Simmons, E. L., to be published.

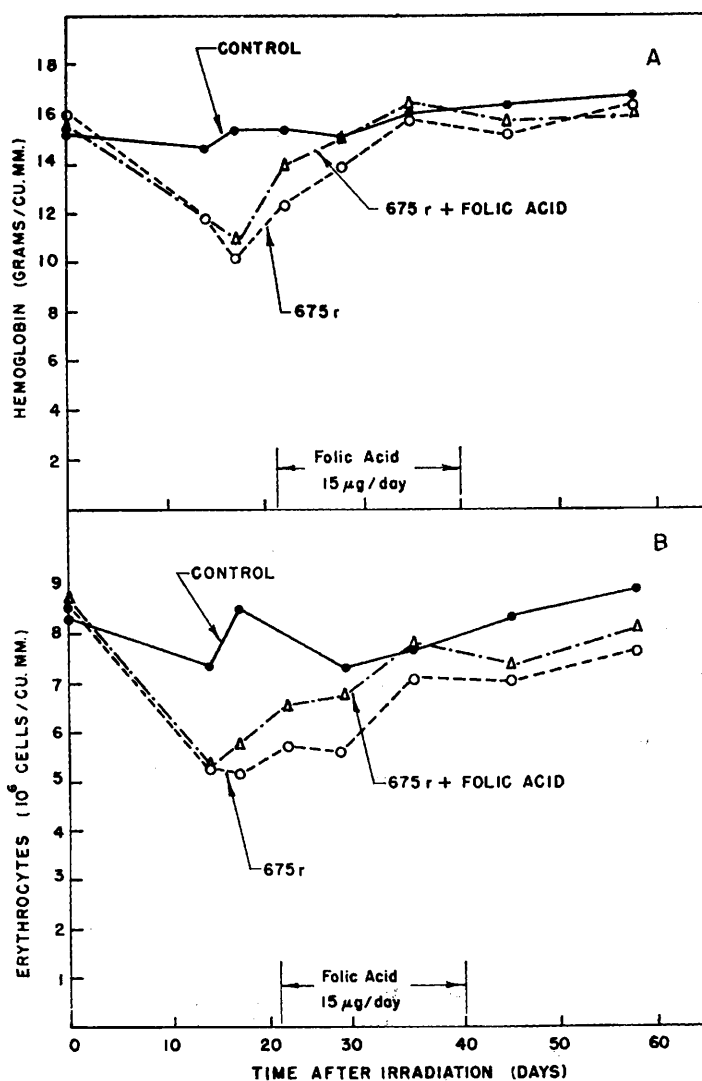


FIG. 1.

Effect of 675 r X irradiation and administration of folic acid on amount of hemoglobin (A) and number of erythrocytes (B) in the peripheral blood.

of interest, therefore, to determine the possible therapeutic effect of folic acid on the macrocytic anemia resulting from total-body X irradiation.

Male white rats were irradiated with 675 r (the approximate median lethal dose). Conditions of irradiation were: 200 Kv, 15 ma, 0.5 mm Cu, and 1.0 mm Al filters, target field distance 72.5 cm, and exposure rate about

16 r per minute. One half of the irradiated animals were given intraperitoneal injections of folic acid daily, 5 days per week. The animals were divided into 3 groups and treated as follows:

Group	No.	Treatment
1	10 (5 blood animals)	Controls
2	10 (5 blood animals)	675 r
3	10 (5 blood animals)	675 r, and receiving 15 µg folic acid per day for the period 22-40 days after irradiation

* Jacobson, L. O., Stearner, P., and Simmons, E. L., *J. Lab. and Clin. Med.*, 1947, **32**, 1425, Abst. 37.

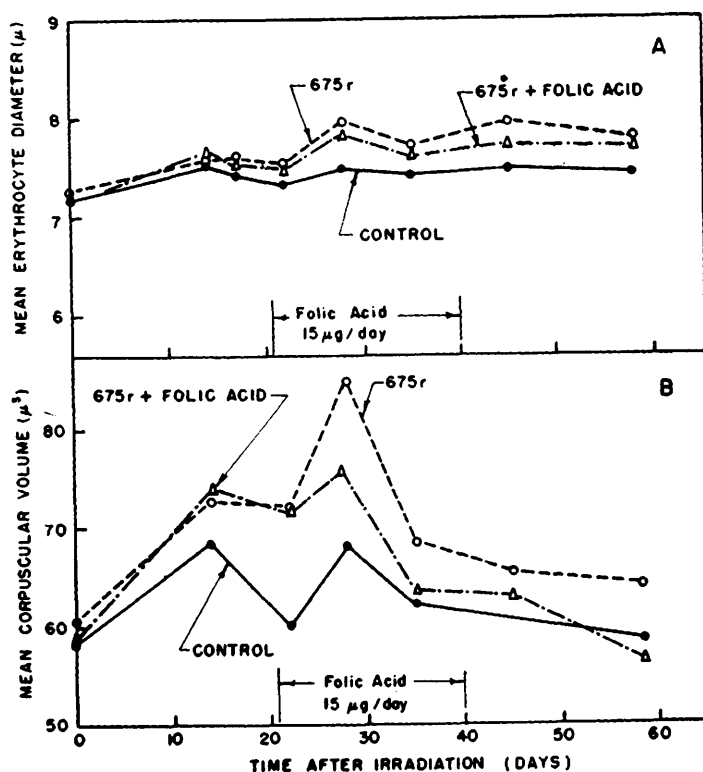


FIG. 2.
Effect of 675 r X irradiation and administration of folic acid on mean erythrocyte diameter (A) and mean corpuscular volume (B).

About 2 weeks after exposure the mean hemoglobin and erythrocyte values in the peripheral blood fell to about 70% of that of the control (Fig. 1). At most sampling intervals the irradiated group that received folic acid showed slightly higher values than the untreated irradiated group. The mean erythrocyte diameter was increased in the irradiated groups at 3 weeks after exposure and persisted for the duration of the observation. Fig. 2 shows the macrocytosis was approximately equal in the 2 irradiated groups and corresponded to the increase in mean corpuscular volume. However, the increase in mean erythrocyte volume was slightly greater in the untreated than in the folic acid treated irradiated group. The greatest increase in per cent of reticulocytes occurred before the maximum mean corpuscular volume was reached (Fig. 3) and therefore could not have caused the increase in mean erythrocyte diameter and

volume. The administration of folic acid had no apparent effect on the reticulocyte response following irradiation.

Analysis of variance⁷ between Group 2 and Group 3, for all sampling periods from 22 to 58 days (inclusive) after irradiation, indicated a significant difference ($P \geq 0.01$) in only the mean erythrocyte count and mean corpuscular volume. (The variance introduced as a result of separate group caging does not affect the statistical results and, for simplicity of presentation, was ignored). The importance of this difference is minimized because the related factors (hemoglobin and mean erythrocyte diameter) did not show a significant difference. It appears, therefore, that there is little or no effect of folic acid upon the erythropoietic system following exposure to X radiation. The damage to the

⁷ Tyler, S., personal communication.

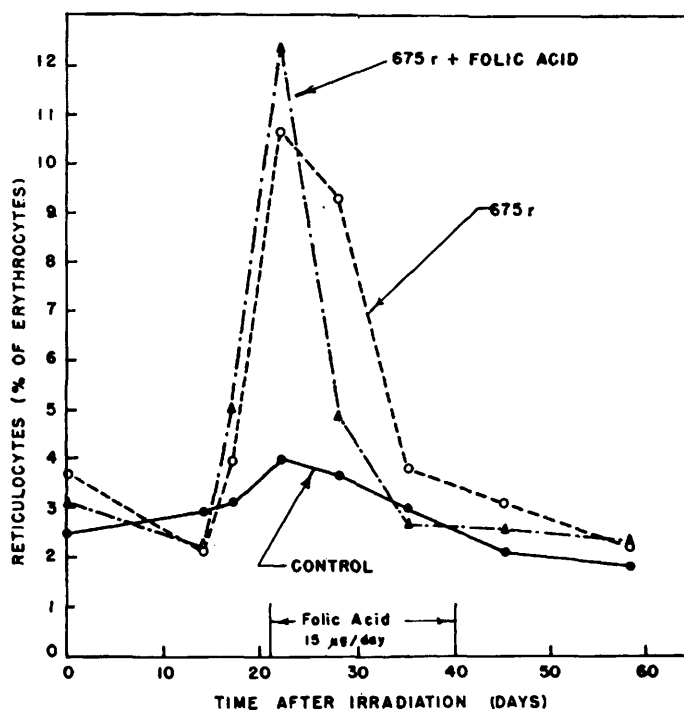


FIG. 3.
Effect of 675 r X irradiation and administration of folic acid on % of reticulocytes in the peripheral blood.

bone marrow is probably caused principally by direct injury. Any indirect damage resulting from damage to the viscera, which

produces the antianemia principle, must be a relatively minor source of injury.

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Genetic Changes in Gastric Lesion and Fibrosarcoma Susceptibilities.*

LEONELL C. STRONG.

From the Department of Anatomy, Yale University School of Medicine.

Evidence has been published that the gene for brown hair has mutated to dominant black several times in the descendants of mice which had been injected with methylcholanthrene for several generations. Concomitant

with the production of these dominant hair color mutations there were also obtained (1) a considerable increase in susceptibility to induced fibrosarcomas, (2) an increased litter size, and (3) increased vitality. All 3 of these characteristics appear to be associated with the black mutant character, never with their brown litter mates. The evidence points toward the production of a widespread germinal change brought about by the effect of methylcholanthrene upon the germ plasm,

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