

the inhibitory effect of 6-MP in tissue cultures of S-180 and of embryo skin(4). It has also been found that the agent inhibits the acetylation of sulfonamide in rat liver homogenates (6).

Summary and conclusions. Chronic treatment with tolerated doses of 6-mercaptopurine causes a reduction of 50% or more in the respiration and anaerobic glycolysis of Sarcoma 180 while it does not impair the metabolic functions in liver and kidney. Succinic dehydrogenase activity of Sarcoma 180 is also impaired by treatment with 6-mercaptopurine, but this effect does not seem to be great enough to account fully for the observed reduction in respiration.

1. Clarke, D. A., Philips, F. S., Sternberg, S. S., and Stock, C. C., *Ann. N. Y. Acad. Sci.*, 1954, v60, 235.
2. Umbreit, W. W., Burris, R. H., and Stauffer, J. F., *Manometric Techniques and Tissue Metabolism*, p119, Burgess Publishing Co., Minneapolis, Minn.
3. Schneider, W. C., and Potter, V. R., *J. Biol. Chem.*, 1943, v149, 217.
4. Bieseke, J. J., *Ann. N. Y. Acad. Sci.*, 1954, v60, 228.
5. Brown, G. B., *Antimetabolites and Cancer*, 1954, A. A. A. S., Washington, D.C., p285.
6. Garattini, S., Morpurgo, C., and Passerini, N., *Giorn. It. Chemioter.*, 1955, v2, 29.

Received July 2, 1956. P.S.E.B.M., 1956, v92.

An Evaluation of Thymidine in Treatment of Tropical Sprue. (22606)

CHARLES E. BUTTERWORTH, JR.* AND ENRIQUE PEREZ-SANTIAGO.†
(Introduced by W. H. Crosby.)

Tropical Research Medical Laboratory, San Juan, P.R., and Department of Hematology, Walter Reed Army Institute of Research, Washington, D.C.

Spies *et al.*(1) demonstrated that thymine given orally in large doses has anti-anemic properties for pernicious anemia patients comparable to folic acid. Vilter *et al.*(2) have noted similar results with uracil. Thymine is capable of replacing folic acid in the growth of a folic acid "dependent" strain, *Lactobacillus lactis*, if vit. B₁₂ is provided(3). Thymidine has been shown to be effective in replacing vit. B₁₂ in the growth of a number of strains of Lactobacilli under conditions in which vit. B₁₂ is ordinarily required(4,5). Thymidine also exerts a marked sparing action on the requirement for folinic acid of *Leuconostoc citrovorum*(3). These results have been taken as evidence that vit. B₁₂ is involved in the linkage of desoxyribose with thymine to produce thymidine. Folic acid participates in the transfer of single-carbon units such as the steps leading to the methyl-

tion of uracil to produce thymine.

Since folic acid and vit. B₁₂ are equally efficacious in the treatment of tropical sprue it seemed of interest to determine the effect of thymidine in the treatment of the megaloblastic anemia of this disease. If there is a block only in the chemical pathways leading to the formation of thymidine, the administration of this end product should correct the defect. To our knowledge there have been no published reports on the use of thymidine in sprue. It has been tried in only small amounts (5 mg) in the treatment of pernicious anemia(6).

TABLE I. Effect of Thymidine on Megaloblastic Anemia of Tropical Sprue.

Patient	Dose (mg)	Route	Total dose (mg)	Reticulocytosis
1	50	I.M.	50	None
2	50	"	50	"
3	100	"	100	"
4	200	I.V.	200	"
5	100	I.M.	600	"
6	100	"	1400	"
7	250	"	2500	"

* Major, M. C., United States Army, Tropical Research Medical Laboratory, San Juan, P. R.

† Bayamon District Hospital, Bayamon, Puerto Rico.

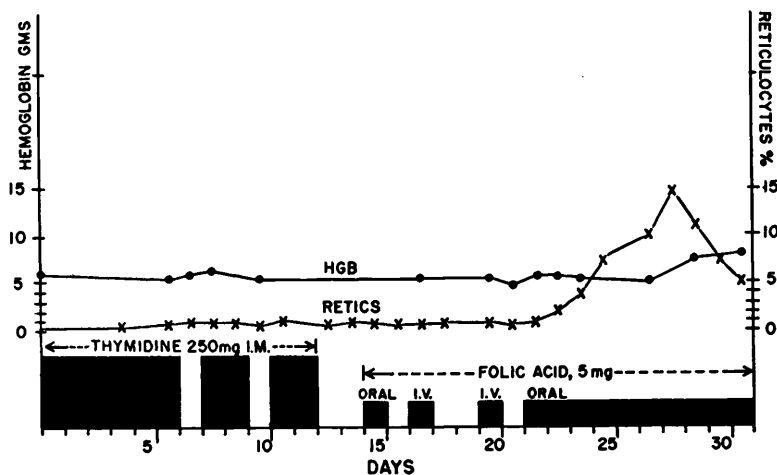


FIG. 1. Serial hemoglobin and reticulocyte values in the patient who received 2500 mg of thymidine parenterally. A reticulocytosis occurred with small amounts of folic acid given orally, but not with thymidine.

Material and methods. Seven patients with tropical sprue were studied. All gave a history of diarrhea, weakness, and weight loss. All had glossitis, malabsorption, marked anemia, and megaloblastic bone marrow. Aqueous solutions of thymidine were sterilized by autoclaving. Bacteriological assay with *L. leichmannii* after sterilization confirmed potency. Paper chromatography after sterilization gave a single spot with an Rf value identical with a non-autoclaved sample of the same material. All doses were given by intramuscular injection, except one which was given intravenously. When multiple dosage was used, injections were given daily or on alternate days. Patients were observed clinically and were followed with frequent reticulocyte counts, and hemoglobin determinations for 2 week periods.

Results. The results are summarized in Table I and Fig. 1. During the observation period none of the patients showed subjective or objective evidence of improvement. Subsequent administration of folic acid in all patients led to a reticulocytosis and rapid clinical improvement. Vitamin B₁₂ is considered to be 10,000 to 30,000 times as effective in promoting growth of *Lactobacilli* as thymidine(7). Thus one microgram of Vit. B₁₂ is equivalent to 10 to 30 mg of Thymidine.

The first 4 patients possibly did not receive a sufficient dose to expect a reticulocytosis. The latter 3, however, received the equivalent of at least 20, 47 and 80 μ g of Vit. B₁₂ by the above criteria, and should have been expected to develop reticulocytosis if thymidine deficit were the sole metabolic defect.

Summary. Injections of a potent preparation of Thymidine in doses equivalent to at least 20, 47, and 80 μ g of Vit. B₁₂ were without effect in producing hematologic improvement in patients with tropical sprue in relapse.

The thymidine used in this study was purchased from Nutritional Biochemicals Corporation.

1. Spies, T. D., Frommeyer, W. B., Vilter, C. F., and English, A., *Blood*, 1946, v1, 185.
2. Vilter, R. W., Horrigan, D., Mueller, J. F., Jarrold, T., Vilter, C. F., Hawkins, V., and Seaman, A., *ibid.*, 1950, v5, 695.
3. Shive, W., *Fed. Proc.*, 1953, v12, 639.
4. Wright, L. D., Skeggs, H. R., and Hulf, J. W., *J. Biol. Chem.*, 1948, v175, 475.
5. Kitay, E., McNutt, W. S., and Snell, E. E., *ibid.*, 1949, v177, 993.
6. West, R., and Reisner, E. H., *Am. J. Med.*, 1949, v6, 643.
7. Shive, W., Sibley, M. E., and Rogers, L. L., *J. Am. Chem. Soc.*, 1951, v73, 867.

Received July 2, 1956. P.S.E.B.M., 1956, v92.