

15154 P

Treatment of Sprue with Synthetic *L. casei* Factor (Folic Acid, Vitamin M).*

WILLIAM J. DARBY AND EDGAR JONES. (Introduced by C. S. Robinson.)

From the Departments of Medicine and Biochemistry, Vanderbilt University School of Medicine, Nashville, Tenn.

The similarities of the sprue syndrome in man to the manifestations of vitamin M deficiency in the monkey^{1,2,3} are obvious. It has been demonstrated that *L. casei* factor is curative for vitamin M deficiency in monkeys.⁴ The availability of synthetic *L. casei* factor⁵ has, therefore, prompted us to try this material in the treatment of 2 cases of non-tropical sprue which have recently been admitted to the Vanderbilt University Hospital. Striking clinical and hematological changes have occurred rapidly following the daily intramuscular injection of 15 mg of this synthetic material† as the sole therapeutic agent. Although remissions do occur in sprue, the results obtained indicate that folic acid may exert a specific effect in the treatment of the disease.

The first case treated was a 51-year-old

* A part of this study was financed through the Tennessee-Vanderbilt Nutrition Project by the Tennessee Department of Public Health, the Nutrition Foundation, Inc., and the International Health Division of The Rockefeller Foundation.

¹ Langston, W. C., Darby, W. J., Shukers, C. F., and Day, Paul L., *J. Exp. Med.*, 1938, **68**, 923.

² Day, Paul L., Langston, W. C., Darby, W. J., Wahlin, J. G., and Mims, V., *J. Exp. Med.*, 1940, **72**, 463.

³ Day, Paul L., *Vitamins and Hormones*, New York, 1944, **2**, 71.

⁴ Day, Paul L., Mims, V., Totter, J. R., Stokstad, E. L. R., Hutchings, B. L., and Sloane, N. H., *J. Biol. Chem.*, 1945, **157**, 423.

⁵ Angier, R. B., Boothe, J. H., Hutchings, B. L., Mowat, J. H., Semb, J., Stokstad, E. L. R., Subbarow, Y., Waller, C. W., Cosulich, D. B., Fahrenbach, M. J., Hultquist, M. E., Kuh, E., Northey, E. H., Seeger, D. R., Sickels, J. P., and Smith, J. M., Jr., *Science*, 1945, **102**, 227.

† We are indebted to Dr. Stanton M. Hardy, Medical Director of Lederle Laboratories, for generous supplies of this crystalline synthetic "folic acid" used in these studies.

white man who was admitted to the Medical Service of Vanderbilt University Hospital on September 24, 1945, with the complaint of sore mouth, diarrhea, weakness and weight loss over a period of 10 months. All criteria generally accepted for the diagnosis of non-tropical sprue were fulfilled. These were glossitis, diarrhea with increased fat in stools (37% of dried wt), marked loss of weight (38 lb), pigmentation of the skin, macrocytic anemia, moderate leucopenia, impairment of absorption as indicated by a flat oral glucose tolerance curve and vitamin A tolerance curve, characteristic gastrointestinal pattern on X-ray examination, and a very low serum carotene. The patient had free hydrochloric acid on gastric analysis. On October 4, 1945, he was started on intramuscular injections of 15 mg of the synthetic *L. casei* factor. Four days later the symptoms of glossitis had disappeared. On the 9th day of such therapy the reticulocytes reached a peak of 15.3% and a marked increase in thrombocytes was noted. The hematological improvement has continued (Table I), accompanied by marked general betterment including regeneration of the lingual papillæ, subsidence of the diarrhea and considerable gain in weight. Oral glucose tolerance and vitamin A tolerance curves became more nearly normal.

The second case is that of a 23-year-old white woman who was admitted to the Medical Service of this hospital on October 15, 1945, with the complaint of diarrhea, sore mouth, and general debility, which had its onset during the third trimester of pregnancy. These symptoms had persisted for 3 months until the time of admission, during which time the patient had lost some 34 pounds below her usual non-pregnant weight. Again, all of the usual criteria necessary for the diagnosis of sprue were fulfilled. Sternal aspiration revealed marrow typical of that seen in sprue

TABLE I.
Hematologic Response of a Case of Sprue Following Administration of Synthetic *L. casei* Factor.

Date	Therapy	Erythrocytes, millions per mm ³	Hemoglobin, g per 100 cc	Reticuloocytes, %	Leucoocytes, thousands
9/24/45	None	1.35	6.5	2.9	4.32
10/ 1	"	1.56	6.0	—	5.75
4	15 mg <i>L. casei</i> factor	1.76	7.0	3.8	4.85
7	"	1.85	7.5	3.4	5.55
11	"	2.35	9.0	11.3	6.00
12	"	—	—	15.3	—
14	"	2.37	9.0	9.1	6.25
19	"	3.88	9.5	4.3	—

and pernicious anemia. Gastric analysis revealed free hydrochloric acid after histamine stimulation. Treatment with 15 mg daily of *L. casei* factor was instituted on October 19, 1945. On the fourth day of treatment reticuloocytes had increased to 16.1% from a pre-treatment level of 3.6%. There was definite subjective improvement during this time. Her progress is being followed.

Castle⁶ has reported that folic acid administered by mouth is without effect in doses up to 3.6 mg daily in patients with pernicious

anemia, and Watson *et al.*⁷ found *L. casei* factor ineffective in the treatment of 8 cases of "refractory anemia." There appear to have been published no previous experiences with this factor in the treatment of sprue.

Summary. The preliminary results here presented demonstrate that two cases of sprue have improved markedly following the parenteral administration of synthetic *L. casei* factor. It is reasonable to attribute the observed improvement to a specific effect of the substance administered, although one can not definitely rule out the possibility of spontaneous remissions in these patients.

⁶ Castle, W. B., Ross, J. B., Davidson, C. S., Burehenal, J. H., Fox, H. J., and Ham, T. H., *Science*, 1944, **100**, 81.

⁷ Watson, C. J., Sebrell, W. H., McKelvey, J. L., and Daft, F. S., *Am. J. Med. Sci.*, 1945, **210**, 463.

15155

Plasma Protein Concentrations in Adrenalectomized Rats Maintained on Sodium Chloride.*

JAMES H. LEATHEM.

From the Department of Zoology, Rutgers University, New Brunswick, N.J.

Adrenalectomy in the rat is followed by a decrease in serum albumin and an increase in serum globulin concentration.¹ Since adrenalectomized rats lose weight and reduce their food intake, it would appear that the serum protein changes are due to partial inanition in addition to mild cortical insufficiency. Furthermore, the adrenalectomized rat is in nega-

tive nitrogen balance.² When 1% sodium chloride is given to adrenalectomized rats as drinking water a body weight increase may be observed, more food is consumed and the negative nitrogen balance is improved.² The salt-maintained adrenalectomized rat is not normal in all respects and in this regard examination of the serum protein levels in a small group of rats revealed a subnormal serum albumin.¹ In the present investigation salt-

* Publication of the Bureau of Biological Research, Rutgers University.

¹ Levin, L., and Leatham, J. H., *Am. J. Physiol.*, 1942, **136**, 306.

² Rubin, M. I., and Kriek, E. T., *J. Clin. Invest.*, 1936, **15**, 685.