was approximately the same in the effusion.

Dogs fed increasingly greater amounts of ANTU during frequent intervals develop a tolerance for large doses of the drug. An increase in the serum α globulin concentration appeared to be a characteristic finding in the development of the tolerance. The plasma cholesterol concentration increased markedly during drug administration and diminished when it was discontinued.

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Folic Acid (Pteroylglutamic Acid)* Studies: Hematologic Remissions in Pernicious Anemia.

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Since the *Lactobacillus casei* factor (folic acid) was synthesized in 1945 by Angier and others,[1] many clinical investigators have clearly demonstrated its effectiveness in the treatment of Addisonian pernicious anemia, the anemia of sprue, nutritional macrocytic anemias and the macrocytic anemias of pregnancy. It has likewise been shown that folic acid is quite effective in producing a complete hematologic remission in certain severe macrocytic hyperchromic anemias of infants which are characterized by poor nutrition, a transient histamine fast achlorhydria and a marked megaloblastic hyperplasia of the bone marrow. The treatment of certain human macrocytic anemias with folic acid (pteroylglutamic acid) has been reported by Darby, Jones and Johnson,[2] Spies and co-workers,[3] Moore and co-workers,[4] Goldsmith,[5] Doan, Wilson and Wright,[6] Zuelzer[7] and others. These extensive studies have been made possible by the chemical identification and synthetic preparation of folic acid (pteroylglutamic acid) in sufficient amounts to permit extensive clinical investigation in several fields. Within the past 12 months we have used synthetic folic acid in treating a great number of different blood dyscrasias. The full report of our investigations will be published in a later communication.

This report deals with the effectiveness of folic acid in the treatment of 4 untreated cases of classical Addisonian pernicious anemia in severe relapse. All of the patients in this group were hospitalized for thorough study and control observations prior to the institution of folic acid therapy. In addition to the usual laboratory procedures for classifying and studying an anemia, sternal marrow aspirations, complete X-ray and fluoroscopic studies of the gastrointestinal tract and gastric analyses were done on each patient. None of these patients exhibited involvement of the central nervous system. A typical hematologic remission is graphically illustrated by the erythrocyte, hemoglobin and reticulocyte response indicated in Chart 1.

* The synthetic folic acid (Folvite) used in this clinical investigation was kindly supplied by Stanton M. Hardy, M.D., Medical Director, Lederle Laboratories, American Cyanamid Company, Pearl River, N.Y.

† The authors wish to express their gratitude to Miss Helen May Holt for her technical assistance in this investigation.

[1] Angier, R. B., and others, *Science*, 1945, **102**, 227.

[2] Darby, W. J., Jones, E., and Johnson, H. C., *J. A. M. A.*, 1946, **130**, 780.

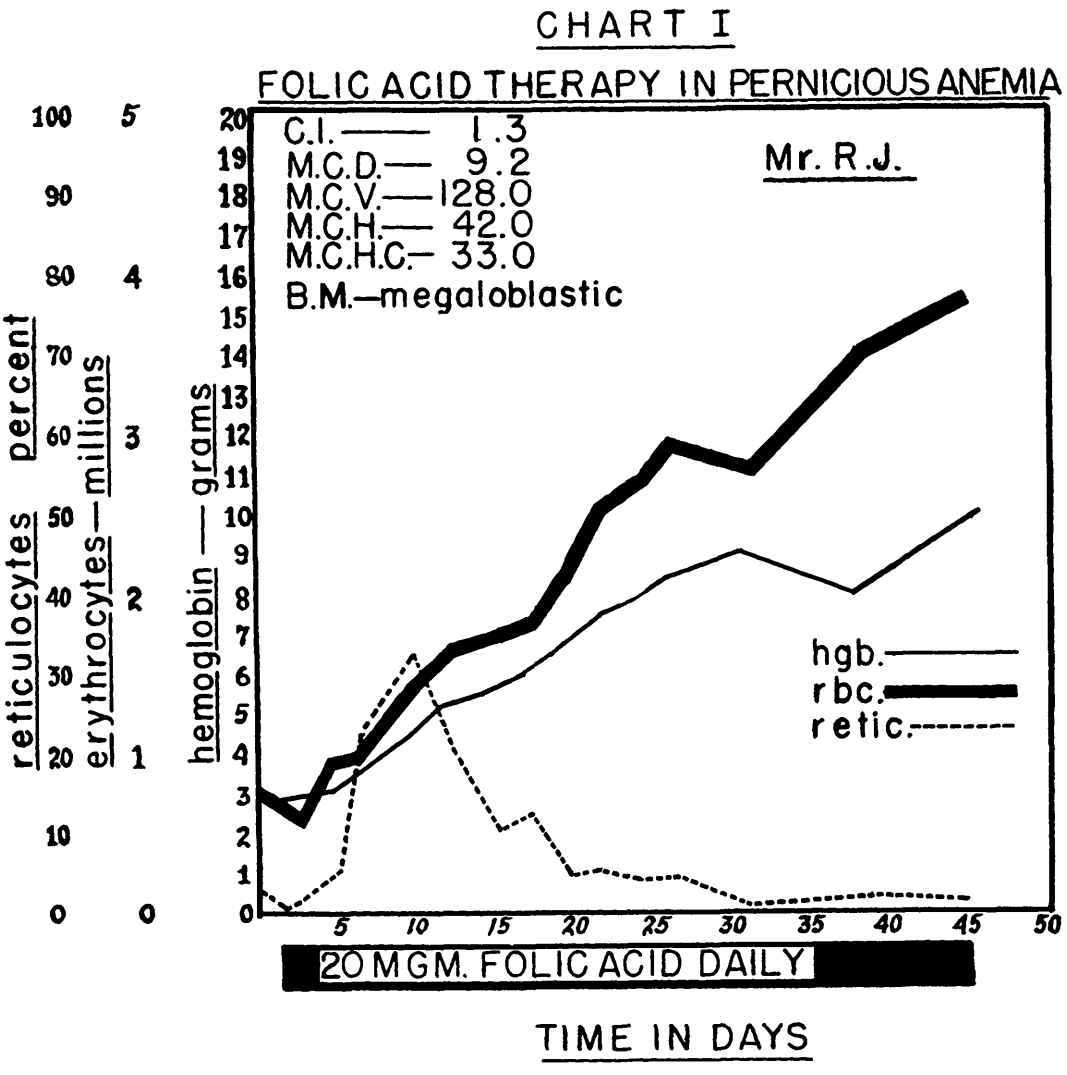
[3] Spies, T. D., Vilter, C. F., Koch, M. B., and Caldwell, M. H., *South. M. J.*, 1945, **38**, 707.

[4] Moore, C. V., Bierbaum, O. S., Welch, A. D., and Wright, L. D., *J. Lab. and Clin. Med.*, 1945, **30**, 1056.

[5] Goldsmith, G. A., *J. Lab. and Clin. Med.*, 1946, **31**, 1186.

[6] Doan, C. A., Wilson, H. E., Jr., and Wright, C. S., *Ohio State M. J.*, 1946, **42**, 139.

[7] Zuelzer, W. W., *J. A. M. A.*, 1946, **131**, 7.



Similar responses were obtained in 3 other cases.

Case Mr. R. J. The initial erythrocyte count was 770,000 cu mm and hemoglobin was 3 g. This patient was given 20 mg of folic acid (pteroylglutamic acid) daily by mouth, and the hematologic response was prompt. At the present time this patient is in a state of complete hematologic remission (7 months later).

Discussion. Subjective and objective clinical improvement appeared to coincide with the time of maximum reticulocytosis. In all of these cases clinical improvement was rapid and equally as good as is ordinarily observed in pernicious anemia patients receiving adequate liver extract therapy. In the folic acid-treated group it appears that maximum reticulocytosis is greatest in those cases with erythrocyte levels below one million. Our group of patients has been maintained on 10 mg of folic acid daily by mouth.

It is clearly evident that folic acid (pteroylglutamic acid) will produce a satisfactory hematologic remission in cases of classical Addisonian pernicious anemia, and it appears that these patients can be maintained in remission on a daily oral dose of about 10 mg. None of our patients on this therapy have had or developed central

nervous system disease, so that complete evaluation of folic acid in that respect cannot be made at this time. However, Doan and Moore[8] independently have recently reported the development and progression of central nervous system disease in pernicious anemia patients while receiving folic acid therapy. Folic acid appears to be equally as effective as liver extract therapy in the treatment of uncomplicated cases of Addisonian pernicious anemia. While folic acid is effective in producing a favorable hematologic remission in cases of pernicious anemia, it is certain that liver extracts contain active material other than this compound, since the potency of such extracts is greater than can be accounted for on the basis of their folic acid content.

Conclusion. 1. Folic acid (pteroylglutamic acid) is as effective as liver extract in correcting the hematologic deficiency in Addisonian pernicious anemia. 2. Further experience is needed before one can evaluate the effectiveness of this factor in preventing development and progression of central nervous system disease.

[8] Doan, C. A., and Moore, C. V., personal communication to R. R. K.

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Effect of Frequency of Hypothalamic Stimulation upon Bladder Response.

BÖRJE UVNAS. (Introduced by H. W. Magoun.)

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Bladder contraction has been observed by many investigators as the result of the stimulation of the hypothalamus (Karplus and Kreidl,[1] Hess[2] and others). From their experiments on cats Kabat, Magoun and Ranson[3] and Magoun[4] concluded that a center for the contraction of the bladder is localized in a region just rostral to the hypothalamus and that fibres from this region run caudalward through the lateral part of the hypothalamus. Relaxation of the bladder was only infrequently observed but points giving inhibitory responses were found in different regions of the diencephalon (Kabat *et al.*[3]) Beattie and Kerr[5] claimed the existence of centers for the increase of bladder tonus in the anterior hypothalamus and for inhibition in the posterior hypothalamus and upper midbrain.

The blood pressure and respiratory responses to hypothalamic stimulation have been shown to be strongly influenced by the frequency of the stimulus (Hare and Geohegan,[6] Bronk, Pitts and Larrabee,[7] Berry, McKinley and Hodes[8]). In the present experiments the effect of frequency of hypothalamic stimulation upon bladder response was observed.

Methods. Twenty-four cats under intravenous chloralose anesthesia (50 mg per kg body weight) were used. The hypothalamus was stimulated by a bipolar electrode, made by cementing together 2 lengths of enameled nichrome wire, and oriented with the Horsley-Clarke technic. A thyratron stimulator (Rahm), delivering impulses within a frequency range of 3.5 to 1000 per second, was

[1] Karplus, J. P., and Kreidl, A., *Arch. ges. Physiol.*, 1909, **129**, 138.

[2] Hess, W. R., *Arch. f. Psychiatr.*, 1936, **104**, 548.

[3] Kabat, H., Magoun, H. W., and Ranson, S. W., *J. Comp. Neurol.*, 1936, **63**, 211.

[4] Magoun, H. W., *Am. J. Physiol.*, 1938, **122**, 530.

[5] Beattie, J., and Kerr, A. S., *Brain*, 1936, **59**, 302.

[6] Hare, K., and Geohegan, W. A., *J. Neurophysiol.*, 1941, **4**, 266.

[7] Bronk, O., Pitts, R. F., and Larrabee, G., *Res. Publ. Nerv. Ment. Dis.*, 1940, **20**, 323.

[8] Berry, C., McKinley, W., and Hodes, R., *Am. J. Physiol.*, 1942, **135**, 338.