How Much Folic Acid Is Safe in Pernicious Anemia?

MAJ. T. W. SHEEHY, M.C.*

In 1931 Wills[1] described a macrocytic anemia in Hindu women which responded to therapy with autolyzed yeast. This observation initiated a series of investigations which culminated in the discovery in the early 1940's of a new group of growth factors with similar chemical and biologic properties.[2-6] Shortly thereafter substances such as the L. casei factor, vitamin M and vitamin B_c were recognized to be probably identical, and chemical identification of the active principle, pteroylglutamic acid, more commonly known as folic acid, soon followed.[7-10]

Even before chemical identification of folic acid, deficiency states cured by crude concentrates of yeast and liver had been described in men, monkeys, rats, insects and microorganisms.[11,12] The first clinical studies employing synthetic folic acid were reported in 1945,[13] and subsequently there were numerous publications dealing with the therapeutic value of folic acid.[14-17] Initially, folic acid appeared to be a new potent hematologic principle effective in megaloblastic anemias of all types. However, its failure to ameliorate or prevent the neurologic complications of Addisonian anemia soon became evident, and its use in this disease was condemned.[18-21]

FOLIC ACID IN MULTIVITAMIN PREPARATIONS

Soon after its discovery, folic acid was added to a number of multivitamin preparations, usually, but not always, in a dosage lower than that used therapeutically. Undoubtedly, the rationale for this measure included the assumption that folic acid may be taken for long periods with complete safety and that it is a vitamin essential for man which may be inadequate in the diet. However, clear distinction between its use as a vitamin supplement (an adjunct to diet) and as a hematinic (meant to cure anemia) was often lacking. Recognition of the inherent danger of masking pernicious anemia by inadvertent folic acid therapy led to a reduction of the dosage of folic acid in many multivitamin preparations available for general prophylactic use (0.25 to 0.5 mg.). It also led to considerable controversy as to whether such amounts may be safely incorporated in vitamin preparations which may be prescribed for long periods.

Proponents have held that modest amounts of folic acid (circa 0.4 mg. per day) are innocuous, since greater amounts are taken in the normal diet. They point out that such "physiologic" dosages fail to induce a hematologic remission in pernicious anemia, but will prevent or relieve anemias due to folic acid deficiency.[22,23]

Advocates of removal of folic acid from preparations not intended for specific therapy question whether any dosage may be deemed safe as long as multivitamin preparations containing folic acid are readily available to the patient who may regulate his own dosage and may take the medication for protracted periods.[24,25] They point to recent instances of permanent neurologic damage in patients with mild or no anemia who were taking folic acid as a combined supplement.[26-28] Whether or not simultaneous vitamin B_{12} therapy would have prevented such catastrophies is not pertinent to their argument for they emphasize the danger of delayed recognition and diagnosis of pernicious anemia.

Because of this controversy, the Food and Drug Administration recently recommended

From the Department of Hematology, U. S. Army Tropical Research Medical Laboratory, APO 815, New York, New York.

* Chief, Medical Division.

that vitamin preparations containing more than 400 μg. of folic acid in a daily dose be sold only on prescription.[29] The critical factor in consideration of safety is whether or not amounts of 400 μg. or less may be therapeutically active* in pernicious anemia, and it is on this point that "to add or not to add" folic acid must be judged. At present, neither the effects of "physiologic (250 to 500 μg.) nor "minute" (25 to 250 μg.) daily doses of folic acid have been studied extensively in patients with megaloblastic anemias, particularly pernicious anemia. Consequently, any attempt to assess the safety of incorporating microdoses of folic acid in vitamin preparations at this time must be based on indirect evidence.

MICRODOSES IN TROPICAL SPRUE

Clinical experience has shown that folic acid is specifically indicated in megaloblastic anemias associated with sprue, infancy, malnutrition and pregnancy.[30–34] Observations made in the treatment of these anemias with folic acid has contributed to our knowledge of the therapeutic effect of this vitamin and to man's daily need for it. Originally, 100 to 200 mg. daily were considered necessary for treatment; later, smaller amounts were found satisfactory. At present, 5 to 20 mg. daily of folic acid are recommended for the treatment of megaloblastic anemias resulting from a deficiency of this vitamin. However, Woodruff and his associates[35] found that as little as 200 to 500 μg. daily of the vitamin, given orally, produced a remission in infants with megaloblastic anemias and similar dosages, 125 to 250 μg. daily, have been used to relieve megaloblastic anemias in patients with cirrhosis and scurvy.[36,37]

These observations with microdoses of folic acid suggested that very little of the vitamin may be required by patients with anemias resulting from a deficiency of folic acid. In order to assess this possibility, we recently used "minute" doses, 25 μg. daily to treat thirty patients with the megaloblastic anemia of tropical sprue. Clinically, these patients were similar to those described by Spies et al.[31] in one of the original treatises on folic acid therapy. These patients were all maintained on a diet of native foods containing ample dietary folic acid-like activity† for three or four weeks without benefit. Thereafter they were treated orally with 25 μg. daily of folic acid, an amount of approximating the folic acid content of early liver extracts used in the treatment of sprue.[38] If a hematologic response was not evident within ten to fifteen days, the daily dosage of folic acid was increased by increments of 25 or 50 μg. every seven days.

The patients were then classified in three groups according to their hematologic response. Group A consisted of eleven patients who responded to 25 μg. of folic acid daily (Fig. 1 and 2). Group B consisted of eight patients who responded hematologically when the daily dosage of folic acid was increased to 100 or 250 μg. daily. In some cases, in both groups, the reticulocyte response was suboptimal and the reversion from megaloblastic to normoblastic erythroid maturation was delayed. Group C consisted of eleven patients who failed to improve on the initial 25 μg. doses; six of these patients failed to respond to increased doses of folic acid ranging from 100 to 250 μg. daily; one patient failed to respond to daily doses of 250 μg. orally and 500 μg. parenterally.

VITAMIN B_{12} LEVELS

One of the factors suspected of contributing to the different hematologic responses of these superficially similar patients was a coexistent deficiency of vitamin B_{12}. In tropical sprue, as in pernicious anemia, the serum vitamin B_{12} level is abnormal, the intestinal absorption of vitamin B_{12} is impaired, even in many asymptomatic treated patients, and either folic acid or vitamin B_{12} can be used to induce a hematologic remission. The serum vitamin B_{12} levels of the patients in group A were found to range from 50 to 200 μμg. per ml., mean 110 μμg. per ml. (Euglena gracilis: normal, 400 ± 150 μμg. per ml.) The serum vitamin B_{12} levels of the eight patients in

* Active should not be confused with effective, as effectiveness is a subjective term qualified differently by different investigators.

† 50 to 100 μg. of "free" folic acid-like activity; 1,000 to 1,500 μg. of "bound" folic acid-like activity daily.

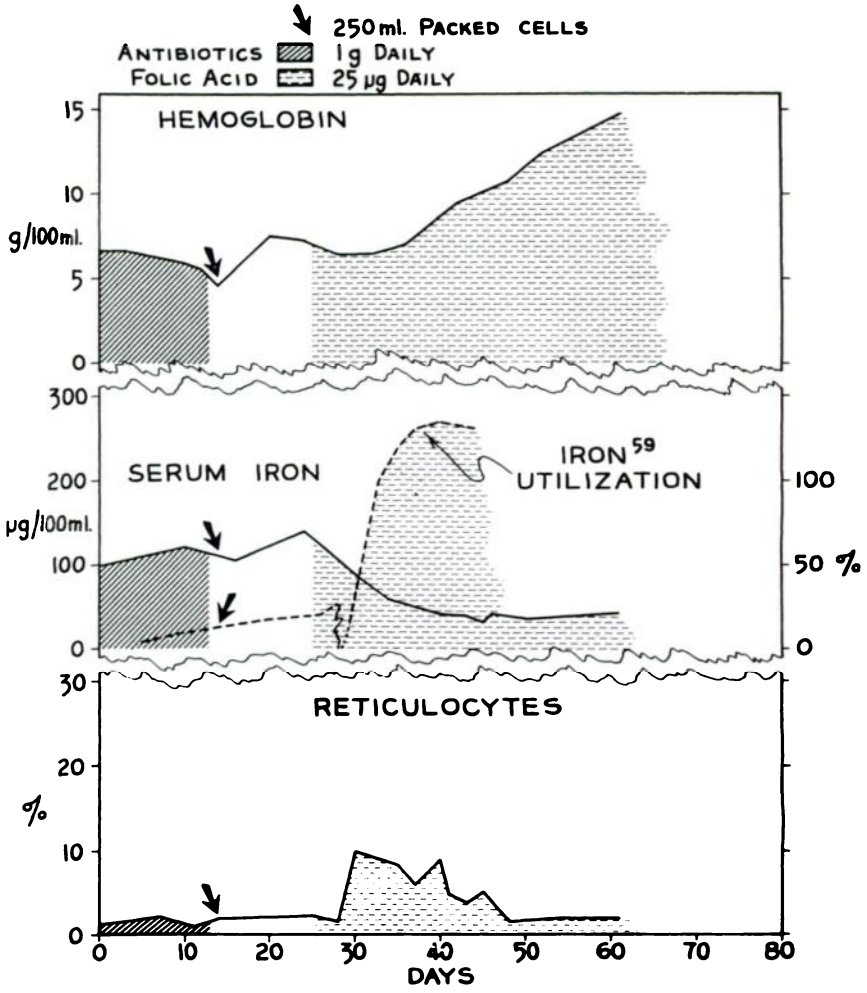

FIG. 1. In this patient, 25 μg. doses of folic acid resulted in a good clinical and hematologic response. The serum iron level fell and the incorporation of Fe^{59} by the red blood cells increased rapidly following the administration of folic acid. The reticulocyte response in this instance was suboptimal.

group B ranged from 25 to 75 μμg. per ml., mean 65 μμg. per ml. The serum vitamin B_{12} levels of the patients in group C ranged from 15 to 90 μμg. per ml., mean 50 μμg. per ml. None of the patients with serum vitamin levels below 50 μμg. per ml. responded to therapy with 25 μg. doses of folic acid, but many responded hematologically to the slightly larger doses (Fig. 3). The patients in group C who failed to respond to the initial dose and to the increased doses of folic acid subsequently responded within eight to fourteen days to parenterally administered vitamin B_{12}, 1 μg. daily. Therapeutically this was further evidence in support of a coexistent vitamin B_{12} deficiency in sprue which may have impeded the hematologic response to folic acid. However, tropical sprue may be complicated by other factors, such as parasitism, hypoproteinemia, and severe malnutrition, any of which may have impaired a response to folic acid.

COMMENTS

The question of the general advisability of incorporating "physiologic" amounts of folic acid in multivitamin preparations cannot be answered from data derived in a study of tropical sprue. This problem concerns the

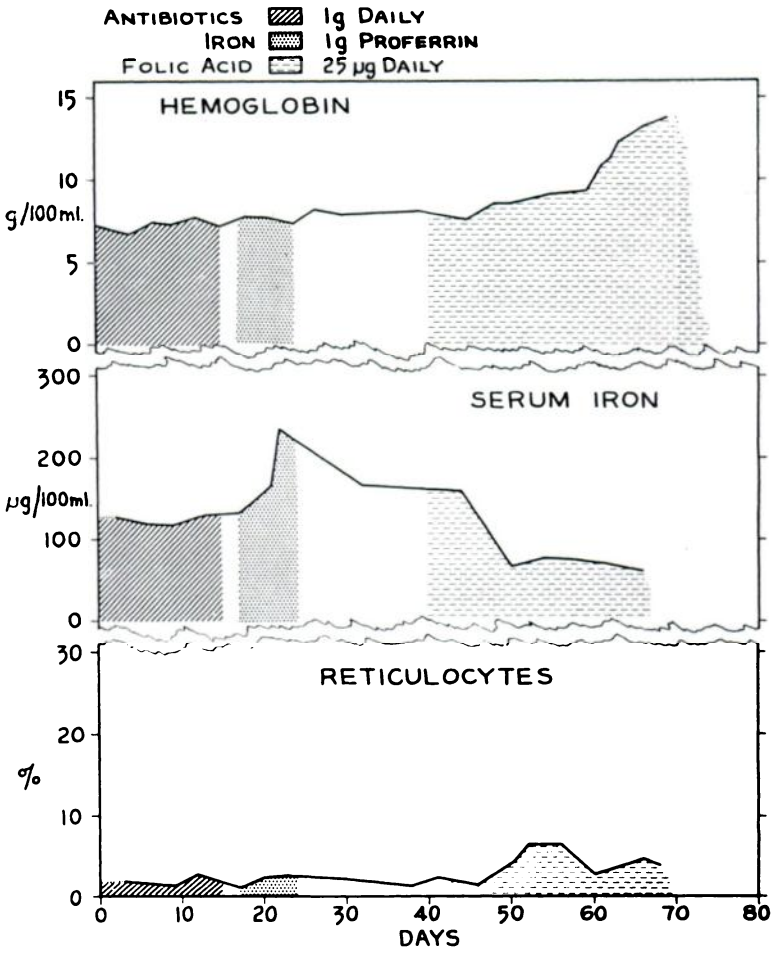

FIG. 2. Clinical improvement was evident in this patient several days after folic acid was administered. Shortly thereafter the patient's hemoglobin level began to rise and eventually reached normal value. A prominent reticulocyte response was never observed. However, in most patients treated successfully with 25 µg. of folic acid daily, the reticulocyte peak varied from 8 to 28 per cent.

safety of multivitamin preparations in the hands of individuals with unrecognized pernicious anemias and at present our knowledge of the action of "physiologic" doses of folic acid in this disease is limited. The concept of the use of "physiologic" doses of folic acid was ingeniously devised to differentiate megaloblastic anemia etiologically.[39] Three patients with pernicious anemia were given 400 µg. of folic acid parenterally daily for ten days. They failed to respond hematologically whereas three patients with megaloblastic anemias resulting from a deficiency of folic acid responded well to the same form of therapy. Unfortunately, this experimental situation was not analogous to the individual with unrecognized pernicious anemia taking a multivitamin preparation for many weeks or months.[25] It did not provide conclusive proof that 0.2 to 0.5 mg. of folic acid daily of this vitamin is harmless in pernicious anemia. It did not prove that such doses are insufficient to mask an incipient megaloblastic anemia while allowing the neurologic lesion of pernicious anemia to progress. Experience gained in the treatment of tropical sprue, albeit not applicable to pernicious anemia, showed that 0.1 to 0.25 mg. of folic acid daily can be active

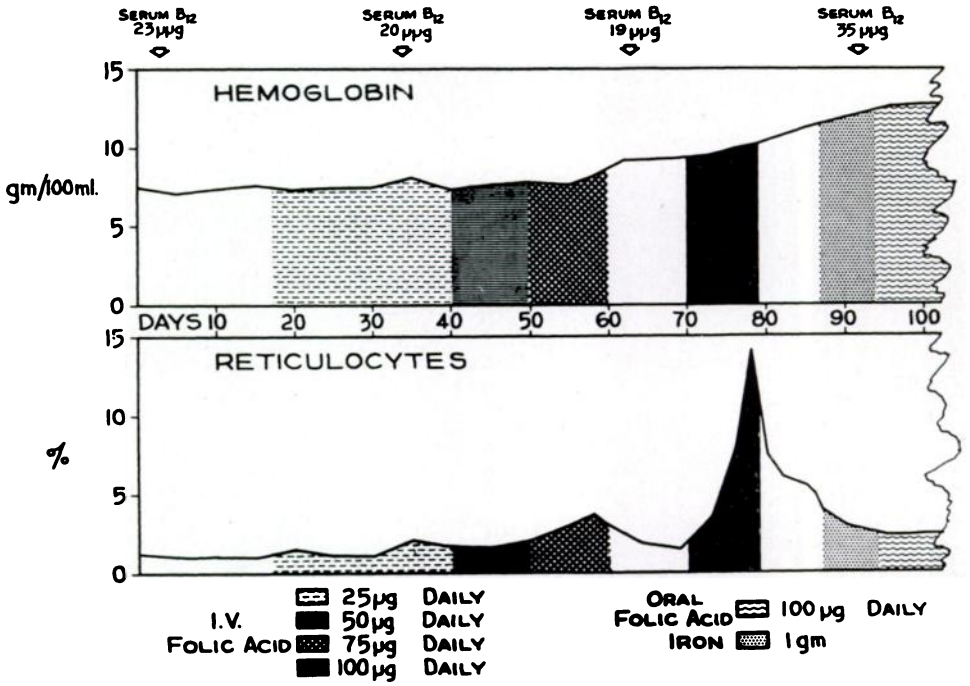

FIG. 3. This patient had a nine year history of sprue and had suffered three previous relapses as a result of discontinuing folic acid therapy. His serum vitamin B_{12} level was found to be low one year prior to his fourth relapse. Oral therapy with 25 μg. folic acid daily did not improve the patient or his blood picture. Thereafter the daily dose of folic acid was given parenterally and was increased by increments of 25 μg. daily every ten days. A hematologic response occurred when the titered dosage reached 100 μg. daily.

in the presence of serum levels consistent with an early deficiency of vitamin B_{12}.[40] These results cannot be dismissed until more patients with Addisonian anemia are treated for more prolonged periods with "physiologic" doses of folic acid. One must question the equanimity with which "physiologic" or "safe" dosage has been recommended. It was for a diagnostic not for a therapeutic purpose that "physiologic" doses were recommended in pernicious anemia.

Considerations of the value of including folic acid in multivitamin preparations must weigh the potential general benefit of the community against the danger to patients with unrecognized vitamin B_{12} deficiency. In tropical areas, particularly in underdeveloped countries where malnutrition is prevalent and medical care inadequate, the incorporation of folic acid into multivitamin preparations may be advisable. Megaloblastic anemias resulting from folic acid deficiency are extremely common in these areas whereas neurologic deterioration due to a deficiency of vitamin B_{12} is exceedingly rare. Here, the general welfare of the populace weighs heavily in favor of such a measure, but in medically advanced communities with more adequate diagnostic facilities this argument loses weight. In such areas, little harm would result from the removal of folic acid from multivitamin preparations until the issue of the effect of microdoses of folic acid in pernicious anemia is solved. In this instance, the general health of the community would not be seriously compromised in protecting a small segment of the populace.

REFERENCES

1. WILLS, L. Treatment of pernicious anemia of pregnancy and tropical anemia: with special reference to yeast extract as a curative agent. *Brit. Med. J.*, 1: 1059, 1931.
2. SNELL, E. E. and PETERSON, W. H. Growth factors for bacteria X. Additional factors required by certain lactic acid bacilli. *J. Bact.*,

39: 273, 1940.
3. Mitchell, H. K., Snell, E. E. and Williams, R. J. The concentration of folic acid. *J. Am. Chem. Soc.*, 63: 2284, 1941.
4. Hutchings, B. L., Bohonos, N. and Peterson, W. H. Growth factors for bacteria. XIII. Purification and properties of an eluate factor required by certain lactic acid bacteria. *J. Biol. Chem.*, 141: 521, 1941.
5. Stokstad, E. L. R. Some properties of a growth factor for Lactobacillus casei. *J. Biol. Chem.*, 149: 573, 1943.
6. Mitchell, H. K., Snell, E. E. and Williams, R. J. Folic acid; concentration from spinach. *J. Am. Chem. Soc.*, 66: 267, 1944.
7. Pfiffner, J. J., Binkley, S. B., Emmett, A. D., Hogan, A. G. and O'dell, B. L. Isolation of antianemic factor (vitamin B_c) in crystalline form from liver. *Science*, 97: 404, 1943.
8. Angier, R. B., Boothe, J. H., Hutchings, B. L., Mowat, J. H., Semb, J., Stokstad, E. L. R., Subba Row, Y., Waller, C. W., Cosulich, D. B., Farenbach, M. J., Seeger, D. R., Sickels, J. P. and Smith, J. M., Jr. Synthesis of a compound identical with the L. casei factor isolated from liver. *Science*, 102: 227, 1945.
9. Peterson, W. H. History of folic acid factors. *Ann. N. Y. Acad. Sc.*, 48: 257, 1946.
10. Cartwright, G. E. Dietary factors concerned in erythropoiesis. *Blood*, 2: 298, 1947.
11. Daft, F. S. and Sebrell, W. H. Successful treatment of granulocytopenia and leukopenia in rats with crystalline folic acid. *Public Health Rep.*, 58: 1542, 1943.
12. The Vitamins, vol. III. Edited by Stokstad, E. L. R., Sebrell, W. H., Jr. and Harris, R. S. New York, 1954. Academic Press.
13. Spies, T. D., Vilter, C. F. and Koch, M. B. Observations of the anti-anemic properties of synthetic folic acid. *Southern M. J.*, 38: 707, 1945.
14. Spies, T. D. Effect of folic acid on persons with macrocytic anemia in relapse. *J.A.M.A.*, 130: 474, 1946.
15. Darby, W. J., Jones, E. and Johnson, H. C. Effect of synthetic Lactobacillus casei factor in treatment of sprue. *J.A.M.A.*, 130: 780, 1946.
16. Zuelzer, W. W. and Ogden, F. N. Folic acid therapy in macrocytic anemia in infancy. *Proc. Soc. Exper. & Biol. Med.*, 61: 176, 1946.
17. Meyer, L. M. Folic acid in treatment of pernicious anemia. *Blood*, 2: 50, 1947.
18. Heinle, R. W. and Welch, A. D. Folic acid in pernicious anemia. Failure to prevent neurologic relapse. *J.A.M.A.*, 133: 739, 1947.
19. Vilter, C. F., Vitter, R. W. and Spies, T. D. The treatment of pernicious anemia and related anemias with synthetic folic acid. I. Observations on the maintenance of a normal hematologic status and on the occurrence of combined system disease at the end of one year. *J. Lab. & Clin. Med.*, 32: 202, 1947.
20. Heinle, R. W., Dingle, J. T. and Weisberger, A. S. Folic acid in the maintenance of pernicious anemia. *J. Lab. & Clin. Med.*, 32: 970, 1947.
21. A warning regarding the use of folic acid, Editorial. *New England J. Med.*, 237: 713, 1947.
22. Eli Lilly and Co. A Case of Misunderstanding. *Physicians Bull.*, 25: 27, 1960.
23. Davidson, C. S. and Jandl, J. H. Editorial: On the Daily Allowance for Folic Acid. *Am. J. Clin. Nutrition*, 7: 713, 1959.
24. Crosby, W. H. The danger of folic acid in multivitamin preparations. *Milit. Med.*, 125: 233, 1960.
25. Crosby, W. H. The daily dose of folic acid. *J. Chronic Dis.*, 12: 583, 1960.
26. Conley, C. L., and Krevans, J. R. New developments on the diagnosis and treatment of pernicious anemia. *Ann. Int. Med.*, 43: 758, 1955.
27. Ross, J. F., Belding, H. W. and Paegel, B. L. Development and progression of subacute combined degeneration of spinal cord in patients with pernicious anemia treated with synthetic pteroylglutamic (folic) acid. *Blood*, 3: 68, 1948.
28. Ellison, A. B. Pernicious anemia masked by multivitamins containing folic acid. *New England J. Med.*, 173: 240, 1960.
29. Status of folic acid in foods for special dietary use and as a drug; extension of effective date of statute for the food additive folic acid. *Federal Register*, 25: 1633, 1960.
30. Darby, W. J., Jones, E. and Johnson, H. C. The use of synthetic Lactobacillus casei factor in the treatment of sprue. *Science*, 103: 108, 1946.
31. Moore, C. V., Bierbaum, O. S., Welch, A. D. and Wright, L. D. The activity of synthetic Lactobacillus casei factor ("folic acid") as an anti-pernicious anemia substance. I. Observations on four patients: two with Addisonian pernicious anemia, one with non-tropical sprue, and one with pernicious anemia of pregnancy. *J. Lab. & Clin. Med.*, 30: 1056, 1945.
32. Vilter, C. F., Spies, T. D. and Koch, M. B. Further studies on folic acid in the treatment of macrocytic anemia. *Southern Med. J.*, 38: 781, 1945.
33. Goldsmith, G. A. The treatment of macrocytic anemia with Lactobacillus casei factor (pteroylglutamic acid). *J. Lab. & Clin. Med.*, 31: 1186, 1946.
34. Spies, T. D., Milanes, F., Menendez, A., Koch, M. V. and Minnich, V. Observations on the treatment of tropical sprue with folic acid. *J. Lab. & Clin. Med.*, 31: 227, 1946.
35. Woodruff, C. W., Peterson, J. C. and Darby, W. J. Citrovorum factor and folic acid in the treatment of the megaloblastic anemia of

infancy. *Proc. Soc. Exper. Biol. & Med.*, 77: 16, 1951.

36. JANDL, J. H. and GABUZDA, G. J., JR. The potentiation of pteroylglutamic acid by ascorbic acid in the anemia of scurvy. *Proc. Soc. Exper. Biol. & Med.*, 84: 452, 1953.
37. JANDL, J. H. and LEAR, A. A. The metabolism of folic acid in cirrhosis. *Ann. Int. Med.*, 45: 1027, 1956.
38. SUAREZ, R. M., SPIES, T. D. and SUAREZ, R. M., JR. The use of folic acid in sprue. *Ann. Int. Med.*, 26: 643, 1947.
39. MARSHALL, R. A. and JANDL, J. H. Responses to "physiologic" doses of folic acid in the megaloblastic anemias. *Arch. Int. Med.*, 105: 352, 1960.
40. SHEEHY, T. W., RABINI, M. E., PERÉZ-SANTIAGO, E., SANTINI, R. and HADDOCK, J. The effect of "minute and titrated" amounts of folic acid on the megaloblastic anemia of tropical sprue. *Blood*, in press.

EDITORIAL COMMENT

As an editorial response to Dr. Sheehy's remarks, first it may be pointed out that his observations that some patients with the megaloblastic anemia of sprue may respond to very small doses of folic acid provides new and important information as to the minimally effective dose of folic acid. Whether these patients, with their multiple deficiencies, including deficiency of vitamin B_{12}, are especially sensitive to folic acid, and whether preliminary therapy with antibiotics may have potentiated their responsiveness, remains to be determined. We look forward to further study of this phenomenon from Dr. Sheehy and his collaborators.

These studies do not particularly bear on the question of what constitutes a "safe" dose level of folic acid in patients with vitamin B_{12} deficiency. The solution to that question must be derived from long-term studies of patients with pure vitamin B_{12} deficiency (pernicious anemia) placed on low doses (i.e., 0.4 mg. or less) of folic acid and compared to a similar group of patients not so treated.

One can make a reasonable argument based on available evidence either for or against the inclusion of small amounts of folic acid (we have recommended 0.1 or 0.2 mg. daily)* in multivitamin preparations. If it can be shown by Dr. Sheehy or others that considerably smaller doses do indeed afford reliable therapy for folic acid deficiency, any potential risk to patients with pernicious anemia could presumably be still further reduced by adopting a lower dose level of folic acid for general use. However, it should be realized that deficiency of folic acid is common; at the Boston City Hospital, at least, it is considerably more frequent than vitamin B_{12} deficiency. In our opinion, it would be a pity to deny this nutrient to the many because of the unproved possibility that small doses of folic acid taken for a long period might mask the clinical picture of some unrecognized cases of pernicious anemia. At present it would seem the lesser of two risks to permit small amounts of folic acid to be included in multivitamins preparations pending further information, than to ban such use prematurely.

JAMES H. JANDL, M.D.
CHARLES S. DAVIDSON, M.D.
Thorndike Memorial Laboratory
Boston City Hospital
Boston, Massachusetts

* DAVIDSON, C. S. and JANDL, J. H. On the daily allowance for folic acid. *Am. J. Clin. Nutrition*, 7: 711, 1959.