Editorial

On the Daily Allowance for Folic Acid

THE DISCOVERY of folic acid (pteroylglutamic acid) is one of the most fascinating stories of modern biology and biochemistry, particularly as so many disciplines, along quite separate roads, came to the same conclusion.[1] The clinical usefulness of this vitamin in treating the anemia of sprue and of other malabsorption states led many to herald it as one of the greatest therapeutic advances in modern medicine. However, since it was found not to be harmless when used in pernicious anemia,[2] voices of caution have been raised and considerable debate has ensued. Gradually the heat from both sides has diminished as more facts have become available concerning the usefulness and potential dangers in man and their relation to dosage. The intention here is to discuss dosage in relation to effectiveness and absence from known harm.

The minimum daily requirement for folic acid is unknown, although some "good guesses" can be made based on the blood response of patients with folic acid deficiency. The anemia due to folic acid deficiency, when severe, is megaloblastic and macrocytic. The cells are well filled with hemoglobin unless concomitant iron deficiency exists. In this country most patients with megaloblastic anemia responding to folic acid fall into the following categories: (1) malabsorption syndromes, especially sprue, (2) megaloblastic anemia of pregnancy (the so-called "pernicious anemia of pregnancy," a misnomer), (3) some severe alcoholics with cirrhosis, (4) some patients with an intestinal blind-loop, (5) some patients receiving anticonvulsant drugs, (6) the megaloblastic anemias of infancy and (7) rarely, in patients also suffering from scurvy.

In true Addison's pernicious anemia, the deficiency (conditioned by lack of intrinsic factor) is of vitamin B_{12}, although occasionally a deficiency (probably dietary) of folic acid may occur also. It is now clearly recognized that administration of folic acid will usually induce a reticulocyte response and at least a partial hematologic remission in pernicious anemia. The remission is usually not permanent and, much more important, folic acid does not prevent the neurologic complications of pernicious anemia and may even induce an exacerbation, possibly by causing the body to use up what little vitamin B_{12} remains. It is essential, therefore, to differentiate those megaloblastic anemias which are due to folic acid from those caused by vitamin B_{12} deficiency before treatment is begun. This usually is not possible on clinical grounds alone. Several measures have been proposed to differentiate these two anemias.

First, one may measure the amount of vitamin B_{12} in the serum. Low concentrations are always found in pernicious anemia and they are usually normal or high in folic acid deficiency.[3] The method is tedious and finicky, however, and is not suitable at present for a general laboratory. Moreover, it tells nothing directly about the state of folic acid nutrition.

Second, one may measure the urinary excretion of folic acid following a standard dose.[4,5] One must be prepared to measure urinary folic acid, not a simple task, and this test requires the administration of folic acid which will give a blood response precluding further study.

Third, when folic acid antagonists are administered, an abnormal metabolite of histidine appears in the urine: formiminoglutamic acid (FIGLU).[6] Formiminoglutamic acid has

been found in the urine of some, but not all, patients with anemia due to folic acid deficiency. The increased excretion of this metabolite does not seem to be a sensitive index of folic acid deficiency and there is evidence that it is not entirely a specific one.[7] The presence of FIGLU in the urine, therefore, does not appear to be an entirely satisfactory test for folic acid deficiency at present.

The fourth measure is the determination of the fasting serum folic acid. Indifferent results have been reported previously, but results with a new method[8] do seem to parallel the clinical degree of folic acid deficiency. The method is microbiologic using L. casei. As with the serum assay for vitamin B_{12}, this valuable technic is still suitable primarily for research laboratories.

Finally, the fifth measure depends upon the differential hematologic response of patients with pernicious anemia and folic acid deficiency to *small* amounts of folic acid and of vitamin B_{12}. The procedure is straightforward but does require careful study of the patient for ten days or more and is applicable only to patients with megaloblastic anemia. So far, six patients have been reported.[9] Three of these, considered to be deficient in folic acid, were given 400 μg. of folic acid parenterally daily with excellent hematologic responses. The other three with classic pernicious anemia did not respond to these amounts of folic acid, but did respond to 15 mg. daily and would undoubtedly have responded to vitamin B_{12}.

The suggestion is made that physiologic amounts of folic acid and vitamin B_{12} given separately will allow a clear distinction between these two diseases by the hematologic response. It is perhaps of interest that this method, depending upon clinical hematologic response, is the classic method (and, formerly, the only reliable method) for assaying liver extract and was that used by Minot and Murphy to test the effectiveness of diet and liver in the treatment of pernicious anemia in 1926. In Castle's hands it made possible discovery of the double deficiency of the intrinsic and extrinsic factors in patients with pernicious anemia.

The question may now be raised concerning folic acid in multivitamin preparations. In the past, some have recommended that no folic acid be included because of the possibility that a "false" remission of pernicious anemia would be inadvertently effected without control of the neurologic complications. It now seems likely, as noted, that patients with pernicious anemia will not respond to administration of small (400 μg. or less) daily doses to which patients with folic acid deficiency respond well. Such an amount might then be considered a reasonable daily dose and approximates the daily amount (300 μg.) recommended by the Council on Foods and Nutrition of the American Medical Association.[10] The National Research Council's Food and Nutrition Board suggested that it would seem probable "that a dietary intake of approximately one-half milligram daily can be expected to cover nutritional needs."[11] Somewhat smaller amounts probably would be satisfactory and in view of the custom of recommending two or three "doses" of a multivitamin preparation daily, perhaps the most suitable quantity in each dose would be in the neighborhood of 100 to 200 μg. The amount of folic acid absorbed from the normal diet is not known with certainty, but it is probably in approximately the same range,[5] most of it being derived from folic acid conjugates which are partially broken down in the gastrointestinal tract.

It would appear, therefore, that small amounts of folic acid in multivitamin capsules (around 200 μg.) would be effective in preventing dietary deficiency of folic acid. Since synthetic folic acid is almost entirely absorbed by the normal intestine,[5] such preparations should also suffice for the treatment of patients with simple dietary deficiency of folic acid without incurring a hazard to patients with undiagnosed pernicious anemia. The presently available oral preparations containing synthetic folic acid alone in larger doses should be reserved by prescription for patients with known intestinal malabsorption or with a specific abnormality in folic acid metabolism such as may exist during prolonged administration of anticonvulsant drugs.

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