

This Week's Citation Classic®

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Klipstein F A. Subnormal serum folate and macrocytosis associated with anticonvulsant drug therapy. *Blood* 23:68-86, 1964.
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The findings published in this paper showed that subclinical folate deficiency can occur in the absence of anemia. More than half of a group of 65 nonanemic epileptics taking anticonvulsant medications had a subnormal serum folate concentration (measured by a microbiological assay) and macrocytosis of the red blood cells. [The SCI® indicates that this paper has been cited in over 165 publications.]

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During the decade between 1950 and 1960, techniques were developed that permitted clarification of the pathogenesis and roles of deficiency of folate and/or vitamin B12 in the development of megaloblastic anemia associated with different disorders. Those for vitamin B12 came first: a serum microbiological assay for deficiency in 1952 and the radioisotopic test of this vitamin's absorption in 1953. Similar assays for folate lagged behind, however, and had not been developed by 1959 when I went to London to spend a year as an NIH trainee in hematology working in David Mollin's laboratory in Sir John Dacie's Department of Haematology at the Royal Postgraduate Medical School (Hammersmith Hospital).

Mollin, who shortly thereafter was to become professor of hematology at St. Bartholomew's Hospital, had gathered together a group of talented

young investigators concerned with the pathophysiology of the megaloblastic anemias. Christopher Booth (later to become director of the MRC Clinical Research Centre, Harrow) and Selwyn Baker (later to become director of the Wellcome Research Unit at the Christian Medical College, Vellore, South India) investigated vitamin B12 absorption, and it was this laboratory that first identified the ileum as site of absorption of this vitamin. I. Chanarin, who later moved to St. Mary's Hospital where he wrote his encyclopedic textbook on the megaloblastic anemias in 1969,¹ used a microbiological assay to study aspects of folate absorption. While there, I joined the group working on the development of a serum assay for folate deficiency. By 1960 such an assay, which used *Lactobacillus casei* as the microbiological test organism, had been developed both in Mollin's laboratory² and in that of Victor Herbert in the US.³

Upon return to the Columbia-Presbyterian Medical Center in New York City in 1960, I applied this new assay to a variety of conditions in which megaloblastic anemia occurs, investigating, in collaboration with John Lindenbaum (who is now at the Harlem Hospital), alcoholism, hyperthyroidism, and hemolytic anemias.⁴

Megaloblastic anemia associated with anticonvulsant drug therapy seemed a likely candidate for study since some 60 cases of this complication had already been described in the literature. The anemia proved to be the result of folate deficiency, the cause of which was—and still is—unknown. It also seemed worthwhile thereafter to investigate the folate status of persons taking anticonvulsants who were not anemic; my study showed the presence of subclinical deficiency in many instances, a result that was subsequently confirmed by similar studies in about 15 other laboratories at last count.

I must admit that I was surprised to learn that this article has been cited so frequently; recent publications on this subject have usually referenced either review or textbook articles for this finding. I can only assume that it has been cited often because of the interest that developed subsequently in the broader subject of the role of subclinical or overt folate deficiency in depressive symptoms among persons taking anticonvulsant medications, neuropsychiatric problems, and in mentation of the elderly.⁵

1. Chanarin I. *The megaloblastic anaemias*. Oxford: Blackwell Scientific. 1969. 1,000 p. (Cited 655 times.)
2. Waters A H & Mollin D L. Studies on the serum folic acid activity of human serum. *J. Clin. Pathol.* 14:335-44, 1961. (Cited 515 times.)
3. Herbert V, Baker H, Frank O, Pasher I, Sobotka H & Wasserman L R. The measurement of folic acid activity in serum: a diagnostic aid in the differentiation of the megaloblastic anemias. *Blood* 15:228-35, 1960. (Cited 115 times.)
4. Lindenbaum J & Klipstein F A. Folic acid deficiency in sickle-cell anemia. *N. Engl. J. Med.* 269:875-82, 1963. (Cited 65 times.)
5. Reynolds E H, Carney M W P & Toome B K. Methylation and mood. *Lancet* 2:196-8, 1984.