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Editorials

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Folic Acid—Preventable Spina Bifida and Anencephaly

One of the most exciting medical findings of the last part of the 20th century is that folic acid, a simple, widely available, water-soluble vitamin, can prevent spina bifida and anencephaly (SBA). Not since the rubella vaccine became available 30 years ago have we had a comparable opportunity for primary prevention of such common and serious birth defects. The many epidemiologic studies that resulted in the identification of the preventive effect of folic acid is a model for the kind of research that needs to be done to identify the causes of and primary prevention strategies for other birth defects, the leading cause of infant mortality in the United States. An overview of this research will let readers appreciate the contribution of the article by Werler et al,¹ which is published in this issue of *JAMA*.

See also pp 1233 and 1257.

Spina bifida and anencephaly are common, serious birth defects. Results of epidemiologic studies during the last 30 years show that the birth prevalence of these birth defects has varied remarkably over time, by geographic location, and by personal factors such as social class and race.² These studies have documented major epidemics, including the great American epidemic that peaked in the 1930s.³ Clues from these studies suggested that environmental agents are important causes of these birth defects.

A variety of nonrandomized epidemiologic studies, the results of which were reported in the 1980s, provided tantalizing clues that suggested that a major environmental factor was nutrition and that one or more vitamins were protective against these birth defects. (See Centers for Disease Control and Prevention report elsewhere in this issue.) The publication, in the summer of 1991, of the Medical Research Council's randomized controlled trial among women who previously had an SBA pregnancy provided definitive evidence that folic acid can prevent SBA.⁴ Since folic acid does not prevent all SBA, I propose that we label SBA that can be prevented by

folic acid as "folic acid—preventable SBA."

On learning of the results of the Medical Research Council trial, the Centers for Disease Control and Prevention began to develop an SBA prevention policy. As a result, in August 1991, the Centers for Disease Control and Prevention issued an interim recommendation for women who had a previous pregnancy affected by a neural tube defect (NTD).⁵

In May 1992, Czeizel and Dudas⁶ presented data from the recently published Hungarian randomized controlled trial, and Werler et al discussed data that are published in this issue of *JAMA*.¹ To the credit of the authors and the editors of the journals in which these studies were subsequently published, data were made available for the public record in the summer so that they could be considered in discussions of public health policy. The results from the Hungarian trial demonstrated that 0.8 mg per day of folic acid in a multivitamin preparation could prevent SBA in a general population with a prevalence rate of approximately two cases per 1000 births. The data of Werler et al suggested that in North America, folic acid supplementation could have prevented a large proportion of SBA between 1988 and 1991. This observation was and continues to be critical to prevention policy decisions. In September 1992, the Public Health Service issued the recommendation that "all women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected by spina bifida or other NTDs."⁷

As important as it is to know that folic acid will prevent SBA, policymakers also want to know how many cases would be prevented if all women received sufficient folic acid. The currently reported rates of SBA in the United States—about one case per 1000 births—are about 80% lower than the five cases per 1000 births found in Boston, Mass, and Providence, RI, in the 1930s.⁸ Werler et al found among recently pregnant women who used folic acid-containing multivitamins daily in the periconceptional period a relative risk of 0.4 for NTDs among their offspring. These findings are consistent with the interpretation that 60% of total SBA is folic acid—preventable SBA. Thus, even though the rates of SBA in this country have fallen considerably in the last 50 years, the proportion of SBA that could be prevented by folic acid supplementation remains substantial.

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The most effective and cheapest way to prevent folic acid-preventable SBA is probably by fortifying a food staple with folic acid. In November, an advisory committee to the Food and Drug Administration recommended developing regulations that would permit appropriate foods to be fortified with folic acid. The Food and Drug Administration is considering such fortification. Currently, women who want to prevent folic acid-preventable SBA can consume daily a vitamin pill containing 0.4 mg of folic acid or eat a serving of a food, such as certain breakfast cereals, fortified with 100% of the US recommended daily allowance of folic acid per serving. They can also increase their intake of folates by eating foods that are rich in folates, such as leafy, dark-green vegetables.

Women should, except under a physician's direction, keep their consumption of folic acid below 1.0 mg per day because doses above this level may be associated with difficulties in diagnosing pernicious anemia. The Public Health Service report suggested: "Women may wish to consult their physicians or other health-care providers (nutritionists, dietitians) about how to best obtain the recommended amount of folic acid, while avoiding excessive consumption. Caution should also be taken to prevent excessive use of multivitamin supplements or fortified foods containing vitamin A, since excess vitamin A may cause birth defects."⁷

We now have the scientific basis to prevent folic acid-preventable SBA, not only in the United States, but also in areas such as Mexico and northern China where the current rates are similar to the Boston/Providence rates in the 1930s. By increasing the consumption of folic acid, we can prevent SBA among thousands of infants around the world each year and thus prevent their unnecessary disability, morbidity, and mortality. Moreover, it is reasonable to expect that prevention programs could, in some areas, have rate reductions in a single year that would be comparable to the reductions that took 50 years in this country.

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