Can Vitamin Supplements Prevent Neural Tube Defects? Current Evidence and Ongoing Investigations

George G. Rhoads, MD, and James L. Mills, MD

National Institute of Child Health and Human Development
Bethesda, Maryland

Neural tube defects (NTDs) have been recognized since antiquity; however, the first detailed description of spina bifida was probably not made until around 1650. Nicholas Tulp, the famous Dutch anatomist painted by Rembrandt, published a detailed description in his Observationes Medicæ.1 His illustration is shown in Figure 1. Later, other well-known anatomists including Morgagni (1761), von Recklinghausen (1886), Arnold (1894), and Chiari (1896) studied the condition.2 Although Morgagni hypothesized that an NTD was a result of reopening of the neural tube after normal closure, most later investigators have believed that primary failure of the neural tube to close is responsible for most NTDs. Because the neural tube is completely closed by the 28th day after conception, the search for etiologic agents clearly should be focused on the period before and immediately after conception.

Since the terminology used to describe malformations of the central nervous system (CNS) can become confusing, some of the more common abnormalities will be defined. Anencephaly is absence of the cranial vault, cerebral hemispheres, and sometimes the entire forebrain. In animals, anencephaly is a result of failure of the anterior (cranial) portion of the neural tube to close. It is generally assumed that the same mechanism is responsible for anencephaly in humans. Encephalocele is the absence of one portion of the skull (cranium bifidum), with herniation of meninges and usually the brain through the defect. Spina bifida is a general term referring to absence of the vertebral arches. Confusion results from the use of the term for a wide range of defects of varying severity. Spina bifida occulta is nonfusion of the vertebral arch, usually without abnormalities of either skin.
or neural tissue. *Spina bifida cystica* is probably a result of failure of the posterior (caudal) neural tube to close. There are dorsal defects of the vertebrae with protrusion of meninges alone, *meningocele*, or more commonly, meninges and spinal cord, *meningomyelocele*. Extensive defects are frequently referred to as *rachischisis*.

The functional impact of these defects depends on whether neural tissue develops normally and on the location of the abnormality. Anencephaly is incompatible with life beyond early infancy. The prognosis for encephalocele depends on the extent of normal brain development inside the skull. Meningomyelocele results in loss of function below the level of the lesion and is frequently associated with hydrocephalus. However, isolated hydrocephalus probably has a different cause and is not considered part of the NTD spectrum. Spina bifida occulta rarely results in any

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**FIG. 1.** Nicholas Tulip's illustration of *Spina Bifida from Observationes Medicæ, 1652.*
abnormality and is generally not reported in epidemiologic studies. Several excellent references are available for more extensive discussion.5–6

The most frequent of the symptomatic NTDs are anencephaly and the various forms of spina bifida. Because of their common embryology, and their co-occurrence both in families and in populations, they are believed in many cases to have a similar cause. In this article we briefly summarize the considerable evidence for an environmental cause of these NTDs, and the more modest evidence that periconceptional vitamin deficiency, especially of folate, may play a role. The genetic contribution to NTD, which is clearly important, is not considered here.

Environmental Factors In the Cause of Neural Tube Defects

The evidence for environmental determinants of NTDs in humans has been accumulating for more than half a century and is now persuasive. A recent review of published rates from around the world2 demonstrates that NTD rates are much higher in the British Isles than in genetically similar populations in former British colonies such as Canada, the United States, and Australia. While some of this difference may be due to the diverse mixture of people in Australia and the New World, it is clear that migration of British and Irish peoples to other continents has been accompanied by a reduction in NTD frequency. Prevalence of anencephalus at birth in reports published between 1961 and 1976 was 2.6 to 3.3 per 1,000 in Scotland, whereas the rate in Canadian Scots was 1.5 per thousand.2 During the same period rates for Ireland were 2.1–4.7 while the rates for Irish in Canada were 1.8 and in Boston were 1.2 per 1,000.7 Within the British Isles there is considerable variation in rates. Highest rates are found in the north and west, lowest in the south and east. While genetic factors may contribute to this difference, diet could also be important. Data from the developing world are sparse, with a surprisingly high rate of 5 per 1,000 reported from a small study of consecutive births in Alexandria.8 High rates have also been reported in Sikhs and in a limited area of Northern China (Emanuel I, personal communication, 1985). Reports from Japan, Taiwan, and Singapore suggest rates of anencephalus similar to those in the lower-prevalence areas of North America, but with much lower rates of spina bifida.8,9 The ratio of spina bifida to anencephalus in various reports has generally ranged between 0.7 and 2.0 except, as noted, in the Orient.

Interpreting differing rates in less developed countries may be difficult first because of uncertainty regarding the completeness of ascertainment and second because of difficulty in separating the contributions of genetic and environmental factors. In the light of the evidence that nutrition can influence NTD rates (to be presented later), it is surprising that developing countries in general do not report higher rates.

In addition to the geographic differences that suggest that environmental factors influence NTDs, there are a number of reports of secular changes in the rates of NTDs in eastern North America. For instance, MacMahon and Yen found a substantial epidemic of NTD in the early part of this century by reviewing hospital records from the Boston and Providence Lying-In Hospitals. Rates in Boston rose from 2.08 per 1,000 births in 1900 to 1904 to 4.69 per thousand in 1930 to 1934. Subsequently, they have decreased to 1.43 (1960–1965).10 Rates in Britain have also been falling in recent years. Such changes have preceded effective screening programs, although some of the continuing downward trend in Scotland has been attributed to such intervention.11 Since change within a single population or in mi-
Evidence for the Role of Periconceptional Vitamins

Several lines of evidence have suggested that nutritional deficiency may play a role in the cause of NTD. Studies in rats have shown that exencephaly or anencephaly can be produced by deficiencies in thiamine, riboflavin, pteroylglutamic acid, pantothenic acid, folate, zinc, or vitamin E. Conversely, excesses of vitamin A, retinoic acid, and zinc and cadmium have also produced the defect in hamsters or rats.2,12 This litany of nutritional influences suggests that in these species, NTD is a non-specific outcome of nutritionally stressed pregnancies, and their relevance to the occurrence of the common NTDs in man is uncertain.

The existing work done in humans has also been less than conclusive. Early work in Great Britain demonstrated clearly that NTD is more frequent in the lower social classes in which diet may be poor.13 A similar trend has been seen in some studies in Canada14 and the United States.7 Increases in frequency were noted when food was scarce in Germany after World War II15 and in Holland following the famine of 1944 to 1945.16

In studies of women with malformed fetuses, Hibbard and Smithells found a positive formimino glutamic acid (FIGLU) excretion test (indicating folate deficiency) in 48 (66%) of 73 women carrying fetuses with CNS malformations as compared with 8 (17%) of 54 controls.17 While these measurements were done at the end of pregnancy, not at the critical period of neural tube closure, they are still of considerable interest. It is not clear from the report whether the FIGLU determinations were carried out in a blind fashion and at the same time for cases and controls. The results lacked specificity since 13 (52%) of 25 women having infants or fetuses with other malformations also had abnormal FIGLU excretion.

Laurence et al. carried out dietary assessments for several hundred women who had had an affected fetus. They then observed these women to ascertain the outcomes of their subsequent pregnancies. All six pregnancies with a recurrent NTD occurred in women whose diets had been judged inadequate.18

Smithells, Sheppard, and Schorah collected blood from more than 900 expectant women in Leeds during the first trimester.19 Values for red cell folate, leukocyte ascorbic acid, riboflavin saturation index, and serum vitamin A were found to be higher in social classes I and II than in classes III–V. Among these women were six with NTD-affected fetuses; comparisons of biochemical parameters between them and other pregnant women revealed decreased red cell folate (p < .001), and decreased leukocyte vitamin C (p < .05). These differences did not appear to be explained by the social class gradient.

On the basis of the foregoing evidence, Smithells and coworkers initiated a trial of vitamin supplementation for the prevention of NTDs.20 In order to obtain enough NTD cases and still keep the required numbers of participants to a manageable level, these investigators planned to enroll women with a previously affected fetus in whom the recurrence risk was estimated to be 3–5%. They sought permission from collaborating hospitals to conduct a randomized trial in these women but were
TABLE 1. Nutrients in Daily Dose of Vitamin Supplement Used in Smithells's Studies as Compared with U.S. Recommended Daily Allowances

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>U.S. RDA</th>
<th>Pregnaniva Forte F*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic acid (mg)</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>1,200</td>
<td>141</td>
</tr>
<tr>
<td>Folic acid (mg)</td>
<td>0.80</td>
<td>0.36</td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>60</td>
<td>75.6</td>
</tr>
<tr>
<td>Nicotinamide (mg)</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Phosphorus (mg)</td>
<td>1,200</td>
<td>109</td>
</tr>
<tr>
<td>Pyridoxine (mg)</td>
<td>2.6</td>
<td>1</td>
</tr>
<tr>
<td>Riboflavin (mg)</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Thiamine (mg)</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Vitamin A (IU)</td>
<td>5,000</td>
<td>4,000</td>
</tr>
<tr>
<td>Vitamin D (IU)</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

*Bencard, Brentford, England.

turned down by several hospital ethics committees, presumably on the basis that it would be unacceptable to withhold vitamins from such women. Consequently, Smithells et al. decided to enroll these women when identified before pregnancy and to use women appearing too late for such enrollment as an unsupplemented control group. They used Pregnaniva Forte F (Bencard, Brentford, England), a commercial multivitamin preparation taken three times daily. The contents of this regimen are shown in Table 1. Their first report, published in 1980, revealed a striking effect: 1 NTD recurrence in 137 fully supplemented mothers and 12 NTD cases in 187 controls. These data were extended in a further series of 254 supplemented and 219 unsupplemented women. The results were similar, 2 recurrences in the supplemented and 11 in the unsupplemented group. The combined results from Smithells' studies are presented in Tables 2 and 3. Overall, the recurrence rate was 0.7% in the supplemented women and seven times higher (4.7%) in the unsupplemented women.

These findings, while impressive, have been criticized on several counts. Some critics feel that they could be spurious because of self-selection of the women, over-representation of high-risk areas (especially Northern Ireland) in the unsupplemented group, and an association between lower social class and lack of supplementation. Smithells et al. have dealt with some of these potential biases in their report. As shown in Tables 2 and 3, neither social class nor geographic differences appear to explain their findings fully. They have also separately analyzed women with two or more previously affected fetuses, an especially high risk group for further recurrence. The results were the same. While these reports could be criticized for not using multivariate analysis to take all of these confounding variables into account at once, it seems unlikely that this would account for the very large difference in recurrence rate between the fully supplemented and unsupplemented groups. Still,

TABLE 2. Neural Tube Defect Recurrences with and Without Periconceptional Vitamin Supplementation by Location of Study Center

<table>
<thead>
<tr>
<th>Area</th>
<th>No. of Prior Affected Infants/Fetuses</th>
<th>With Vitamin Supplements</th>
<th>Without Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of Pregnancies</td>
<td>No. with NTD</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>1</td>
<td>139</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2 or more</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Northern England</td>
<td>1</td>
<td>148</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2 or more</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Southeast England</td>
<td>1</td>
<td>119</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2 or more</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>454</td>
<td>3 (0.7%)</td>
</tr>
</tbody>
</table>

Data adapted by permission from Smithells et al. 20,21
TABLE 3. Social Class Distribution of Neural Tube Recurrences

<table>
<thead>
<tr>
<th>Social Class</th>
<th>With Vitamin Supplements</th>
<th>Without Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Preg.</td>
<td>With NTD</td>
</tr>
<tr>
<td>I and II</td>
<td>143</td>
<td>0</td>
</tr>
<tr>
<td>III nonmanual</td>
<td>60</td>
<td>1</td>
</tr>
<tr>
<td>III manual</td>
<td>176</td>
<td>2</td>
</tr>
<tr>
<td>IV and V</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Unemployed and unclassified</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

Data adapted by permission from Smithells et al.21

such an analysis would seem worthwhile to estimate the magnitude of the putative beneficial effect of periconceptional vitamin supplementation.

Some observers have argued that the recurrence rate for NTD in the United Kingdom in recent years has been approximately 2.9%.22,25 Since this is near the mean risk (2.5%) for the total population studied by Smithells et al., it could be argued that their data do not show a real reduction in the occurrence of NTD, but only a partitioning of the population between high-risk and low-risk women through their self-selection for study enrollment. However, the 2.9% figure is heavily based on data from Southeast England, which has relatively low rates and may not be comparable for the mix of patients studied by Smithells.

Enthusiasm for Smithells’s regimen should, perhaps, be tempered by the possibility that vitamins could cause some harm. As noted previously, excesses of vitamin A, retinoic acid, zinc, and cadmium have produced NTDs in hamsters or rats. Retinoic acid is known to be teratogenic in man. Smithells et al. reported 11 non-NTD major malformations in their 454 fully supplemented women. In the two largest centers the rates for these other malformations were 1.8% in the unsupplemented and 2.1% in the supplemented women, a difference that was not statistically significant.24 While this appears reassuring, the possibility of harm is one of the arguments for a randomized trial.

The British data present a prima facie case for the protective effect of periconceptional vitamins. The findings have been reproduced in a second series of women (but, curiously, not in a smaller third series)23 and have been shown to persist after accounting for several of the most important confounding issues. The core of the controversy revolves around the likelihood that women who were organized and cooperative enough to get into the preconceptional supplementation program were at inherently much lower risk of recurrence than those who failed to get involved in a timely manner. There is room for debate about the probable magnitude of this self-selection effect, but there are few documented instances in the medical literature in which it has produced a gradient of risk as high as sixfold.

Folate

Among the many vitamins that might play a role in the causation of NTD, folate has received the most attention. Folate deficiency is known to occur in Western societies and, as noted previously, red cell folate levels were shown to be low in six women who subsequently were found to have NTD-affected fetuses.19 The social class gradient in red cell folate levels demonstrated among pregnant women in Britain would be consistent with the higher rates of NTDs occurring in social classes III–V. The folate antagonists aminopterin and methotrexate have sometimes been
used as abortifacients, and a number of reports of malformations in these cases have appeared. Among 13 such reports, only three women were alleged to have been exposed before 35 days. One of these patients had an anencephalic fetus and the other two, who also received the drug later in pregnancy, had fetuses with less severe skull deformities, low set ears and, in one case, cleft palate. A fourth case treated "in the first trimester" had multiple severe malformations. Among the other nine reports there was one meningoencephalocele after exposure at 63–67 days and two cases of hydrocephaly also with exposure after the neural tube would normally have closed.

If folate deficiency were an important cause of NTDs, one would expect to find a high incidence of NTDs in the offspring of women with folate deficiency megaloblastic anemia. Surprisingly, several case series have not mentioned any association. Pritchard et al. reported on 86 offspring of folate-deficient mothers among whom there were no NTDs. A report of 335 such cases seen at Stoke-on-Trent in England noted the frequency of fetal malformations to be almost identical to that seen in other hospital deliveries. No increase in the NTD rate was mentioned by Varadi et al., who noted that the stillbirth rate was 2% for offspring of affected mothers as compared with 2.6% for unaffected mothers. On the basis of these reports, Pritchard et al. concluded that "it seems quite unlikely that widespread public health measures focused on eradicating all suspicions of folate deficiency by providing folic acid supplement very early in pregnancy or even before conception would have a profound effect on reducing perinatal mortality or congenital malformation in the United States."  

This negative evidence notwithstanding, Laurence et al. undertook a randomized trial of high-dose folate supplementation among Welsh women. They visited 905 women under 35 years of age who had given birth to an affected fetus between 1954 and 1969. One hundred eleven of these women (12.3%) agreed to take part in a blinded prospective randomized controlled trial that would consist of taking either 2 mg folic acid or placebo twice a day starting at the time contraceptives were discontinued. Sixty women were randomized to foleate supplementation and 51 to placebo. Compliance was monitored by measuring serum folate at the 6th to 9th week of estimated gestation and was considered adequate if the serum folate concentration was higher than 10 μ/liter. One woman with a serum folate of 212 μ/liter was classified as a noncomplier after she admitted (at the end of the study) that she had taken a large number of tablets at 7 weeks' gestation, just before her study visit. This patient was one of the two noncompliers shown in Table 4 to have had a fetus with an NTD. Overall, only these two recurrences occurred in the folate-supplemented group as compared with four in the placebo group, a difference that is not statistically significant. The randomization process provides some assurance that these two groups were comparable in terms of other (nonfolate) characteristics, but with the high rate of noncompliance, the results were equivocal. Laurence argued that the noncompliers should be added to the placebo group since they did not receive supplementary folate. An analysis of this type yields results that just reach statistical significance (p < .04) but destroys the comparability of the

<table>
<thead>
<tr>
<th>Outcome of Pregnancy</th>
<th>Folate Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Compliers</td>
<td>Noncompliers</td>
</tr>
<tr>
<td>Normal fetus</td>
<td>44</td>
<td>14</td>
</tr>
<tr>
<td>Fetus with NTD</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>16</td>
</tr>
</tbody>
</table>

Reproduced by permission from Laurence et al. 18
groups, since in many randomized trials those who fail to comply are at higher risk. Thus, because of the small size of the trial and the unorthodox analysis required to produce a statistically significant result, the evidence provided in favor of the folate hypothesis must be considered quite limited.

Ongoing Studies

The evidence that vitamins may prevent NTDs, while intriguing, is in a number of respects incomplete. Because of the problems of self-selection in Smithells's study, many investigators remain unconvinced that vitamins play a crucial role in the prevention of NTD. Moreover, even if the data could be taken at face value, it is not clear a) which vitamin or combination of vitamins is crucial and b) whether the excellent results reported in the prevention of recurrence of NTD would apply equally to women who have not previously had an affected fetus, that is, the general population of women hoping to become pregnant. It is also unclear whether such prevention will work only in a high-incidence area such as Great Britain or whether it would be efficacious in the United States and other lower-incidence countries.

A number of further studies are being undertaken to try to resolve these issues. The most ambitious attempt to replicate and clarify the work of Smithells and Laurence is being undertaken by the Medical Research Council of Great Britain, which has funded a multicenter randomized trial. Women with a prior affected pregnancy are randomized into one of four groups, each of which receives calcium and iron. Additional supplements are allocated as follows: group 1, nothing additional; group 2, multivitamins without folate; group 3, high-dose folate (4 mg); and group 4, multivitamin and high-dose folate combined. Because of this factorial design, it will be possible to compare the two groups with high-dose folate against the two without as well as to compare the two with multivitamins against those without. No data on low-dose folate will be generated.

Since vitamin supplementation in these doses is widely viewed as completely safe, the British trial has been vigorously challenged by those who feel that all women with a prior affected fetus should be offered supplements. The effect of this controversy on recruitment is not yet clear, but the trial may not be large enough to detect a modest but important benefit such as a reduction in NTD rates of 40%. Moreover, even if a benefit is confirmed, it would remain uncertain whether the findings would apply to women who have not had an earlier affected pregnancy.

Trials of the sort being undertaken by the Medical Research Council are best done in high-incidence areas, not only because the high rates provide many potential subjects who have had an affected fetus, but also because recurrence rates are probably higher in such areas and result in a smaller sample size requirement. Besides Great Britain, Ireland is another logical place to mount such a trial, and a study is underway there too. Because of the ethical issue surrounding nonsupplementation of women who have already had an affected pregnancy, the Irish have elected to omit this group. Their trial has only three arms, vitamins without folate, low-dose folate, and both together. Thus, they will be able to compare the recurrence rates in the two groups with folate against the group with multivitamins only and the two groups with multivitamins against the group with folate only. Despite the high rates of NTD, Ireland is a small country and is likely only to be able to recruit enough cases to detect a large preventive effect of folate or multivitamins. In these recurrence trials it is necessary to recruit women before they get pregnant in order to be sure that they are supplemented in very early gestation. Ob-
viously, this adds to the difficulty of carrying them out successfully.

A unique primary prevention trial is being undertaken in Hungary, which has NTD rates between those in Britain and the United States. Czeizel is using a series of clinics to counsel couples hoping to have a first child in order to recruit participants for a randomized trial of the use of vitamins to prevent the first occurrence of NTD. They expect to randomize approximately 10,000 women between a commercial prenatal vitamin preparation (Elivit Prenatal, Roche Laboratories, Nutley, NJ) that includes folate and 17 other vitamins and minerals and a “placebo” containing vitamin C, calcium, copper, manganese, zinc, and lactose. Assuming an incidence of 0.3% in the placebo group, a trial of this size should have an 80% chance of detecting a two-thirds reduction in incidence. A lesser benefit might be missed.

The lower rates of NTDs in the United States make it a less favorable place than the British Isles to undertake prospective studies. The Center for Disease Control is exploring the feasibility of undertaking an American recurrence trial, but it is uncertain whether such a study can be successfully mounted. An interesting feature of the U.S. environment that has an impact on the current subject is the widespread use of multivitamins in women of child-bearing age. The Food and Drug Administration estimates that approximately 40% of women in this age group take some sort of vitamins or supplements and that 12% actually take 0.4 mg or more of folate (the RDA for nonpregnant women). We reasoned that if multivitamins are truly protective, those women who take them regularly should have fewer NTDs. Thus, a retrospective (case-control) study appeared to be a logical approach to the vitamin-NTD hypothesis in the United States. Such a study has been organized by the National Institute of Child Health and Human Development in collaboration with Northwestern University in Illinois and with the State Health Department in California. An attempt will be made to identify as many NTD cases, both prenatal and postnatal, as possible in both of these states. Two sets of control women will be used as a basis of comparison for the frequency of vitamin use in the periconceptional period. One set will be women matched for race and geographic location who have had a normal pregnancy recently completed (for the postnatal cases) or in progress (for the prenatal cases). A second set of controls with abnormal fetus/infant outcomes will also be used to control for recall bias. Within 4 months of termination of pregnancy all subjects will be questioned by telephone about periconceptional vitamin use.

The main potential difficulties in this approach are inaccurate recall of vitamin intake for the period around the beginning of pregnancy and the problem of self-selection of women choosing to use these supplements. It is worth noting, however, that the self-selection process is likely to be different for women choosing to take supplements on their own (often without regard to medical advice) as compared with that in Smithells' studies. In the latter, self-selection was largely for women who are well connected to the medical care system. In the event that the case-control studies show a modest benefit it will be difficult to ascertain whether this is related to self-selection or to a biologic effect of vitamin supplementation. On the other hand, a strongly positive result such as Smithells obtained would be quite suggestive of benefit and would begin to provide useful information about the prevention of first occurrences of NTD as opposed to only the recurrence problem. A completely negative result, with no difference between groups, would also be of interest. Since the suspicion is that women who take vitamins are likely to be of higher social class and lower risk for NTD than other women, a
finding of no difference would have to be viewed as occurring in spite of this potential bias rather than because of it. Because it is possible to recruit many more NTD cases with the retrospective approach than the prospective trials, the statistical power for ruling out a modest benefit is better.

**Current Recommendations**

Until the results of these further studies become available, obstetricians will need to advise patients on the basis of the existing incomplete information. Since it is not clear that the data obtained in the British recurrence trials can be extrapolated to women who have never had an affected fetus, it would seem premature to suggest vitamin supplementation for the average woman hoping to become pregnant. But for women with a prior affected fetus, many clinicians will choose to recommend vitamin supplementation on the grounds that it might be helpful and is presumably safe. We believe that a daily multivitamin, perhaps in divided doses, beginning a month or more before the date of intended conception and continuing through the second missed period, is the most logical supplementation plan. However, a no supplementation option is, in our view, also defensible. Neither Smithells's nor Laurence's findings have yet been independently replicated, and it is entirely possible—some would say likely—that future studies will not reproduce their results. These concerns are especially relevant to low-prevalence areas such as the United States where vitamin deficiency may be less common then in Europe. Physicians and patients who prefer not to use unproven remedies could reasonably extend this view to the vitamin-NTD hypothesis and wait for confirmatory evidence.

**References**