Medical Progress

NEURAL-TUBE DEFECTS

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EACH year spina bifida and anencephaly, the two most common forms of neural-tube defects, occur in 1 in 1000 pregnancies in the United States1 and an estimated 300,000 or more newborns worldwide.2 Although these severe conditions have been recognized since antiquity, never before has progress been so fast and substantive, particularly in the area of prevention. The results of randomized trials indicate that at least half the cases of neural-tube defects could be prevented if women consumed sufficient amounts of the B vitamin folic acid before conception and during early pregnancy.3,4 Elsewhere in this issue of the Journal, Berry et al.5 report the results of a population-based intervention study, which confirmed the effectiveness of folic acid in a community setting.

Increasingly, new findings are unmasking the biochemistry, developmental biology, and molecular genetics underlying neural-tube defects and promise to make possible further strategies for prevention. At the same time, critical issues confront medical professionals and the public. For example, the full potential of folic acid to prevent these disorders has not been realized, despite fortification of cereal products with folic acid in the United States6 and despite recommendations by the Institute of Medicine7 and the Public Health Service8 that women who could become pregnant consume 400 µg of folic acid daily. Preventable disabilities continue to occur, and the underlying cause of neural-tube defects still remains unknown in most cases.

In this review, we shall emphasize recent findings and the contributions of epidemiologic, experimental, and clinical research to the understanding of neural-tube defects. Topics such as animal models9,10 and prenatal diagnosis11 are beyond the scope of this article.

CLINICAL AND DEVELOPMENTAL FEATURES

Although most studies of neural-tube defects have considered only anencephaly or spina bifida, the clinical spectrum also includes encephalocele, craniorachischisis, and iniencephaly (Fig. 1).12 The latter two types are rare, but they tend to occur with disproportionate frequency in areas that have a high rate of neural-tube defects, such as northern China. In northern China, for example, the proportion of infants with neural-tube defects who have craniorachischisis or iniencephaly is 10 times as high as that in the United States.13 Spina bifida occulta, the mildest form of spinal dysraphism, is rarely included in studies of neural-tube defects, because it often remains undetected and because of uncertainty concerning its relation to overt spina bifida12 (Fig. 2). Neural-tube defects can also be classified as open, if neural tissue is exposed or covered only by membrane, or as closed, if the defect is covered by normal skin.14 Approximately 20 percent of affected infants have additional congenital anomalies. Chromosomal abnormalities, single-gene mutations, and teratogenic causes are identified in fewer than 10 percent of affected infants.15

The development and closure of the neural tube are normally completed within 28 days after conception,16 before many women are aware that they are pregnant. It is generally accepted that neural-tube defects are caused by the failure of the neural tube to close, although it has also been suggested that a closed tube may reopen in some cases.17 The embryologic basis of the clinical variation in neural-tube defects is poorly understood (Fig. 1). It has been proposed that in humans, as in mice,18,19 closure of the neural tube occurs at several sites and that the clinical types of neural-tube defects differ depending on the site at which closure fails. Variations in the cellular mechanisms of closure at various sites might also underlie the clinical variation in neural-tube defects, as could differences in sensitivity to factors such as the type and time of exposure to teratogenic agents.16 The genetic controls of the cellular mechanisms of closure have yet to be determined, although several possibly associated genes have been identified in animal models.20

THE BURDEN OF DISEASE

Anencephaly and spina bifida are important factors in fetal and infant mortality.21-23 Each year in the United States, approximately 4000 fetuses are affected, at least one third of which are lost as a result of

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Figure 1. Features of Neural-Tube Development and Neural-Tube Defects.

Panel A shows a cross section of the rostral end of the embryo at approximately three weeks after conception, showing the neural groove in the process of closing, overlying the notochord. The neural folds are the rising margins of the neural tube, topped by the neural crest, and demarcate the neural groove centrally. Panel B shows a cross section of the middle portion of the embryo after the neural tube has closed. The neural tube, which will ultimately develop into the spinal cord, is now covered by surface ectoderm (later, the skin). The intervening mesoderm will form the bony spine. The notochord is regressing. Panel C shows the developmental and clinical features of the main types of neural-tube defects. The diagram in the center is a dorsal view of a developing embryo, showing a neural tube that is closed in the center but still open at the cranial and caudal ends. The dotted lines marked A and B refer to the cross sections shown in Panels A and B. Shaded bars point to the region of the neural tube relevant to each defect.

In anencephaly, the absence of the brain and calvaria can be total or partial. Craniorachischisis is characterized by anencephaly accompanied by a contiguous bony defect of the spine and exposure of neural tissue. In open spina bifida, a bony defect of the posterior vertebral arches (in this case, the lower thoracic vertebrae) is accompanied by herniation of neural tissue and meninges and is not covered by skin. In iniencephaly, dysraphia in the occipital region is accompanied by severe retroflexion of the neck and trunk. In encephalocele, the brain and meninges herniate through a defect in the calvaria. In closed spina bifida, unlike open spina bifida, the bony defect of the posterior vertebral arches (in this case, the lumbar vertebrae), the herniated meninges, and neural tissue are covered by skin.
spontaneous or elective abortion. All infants with anencephaly are stillborn or die shortly after birth, whereas many infants with spina bifida now survive, usually as a result of extensive medical and surgical care. The risk of early death among infants with open spina bifida varies considerably worldwide, depending not only on the severity of the lesion but also on such factors as the availability, use, and acceptance of medical and surgical treatment. For example, the estimated rate of death among affected infants in rural areas of northern China is nearly 100 percent, whereas in the Netherlands it is 35 percent and in the United States it is 10 percent. Determining the long-term prognosis is also difficult because of improved management of some medical complications (e.g., renal failure) that previously substantially increased the risk of death among adults with spina bifida. Two studies documented survival to nearly the third decade of life in 52 percent and 68 percent of affected persons in whom the defect was surgically repaired shortly after birth.

Infants with spina bifida who survive are likely to have severe, life-long disabilities and are at risk for psychosocial maladjustment. Medical problems may often result from the neurologic defect or from its repair (e.g., paralysis, hydrocephalus, Arnold–Chiari type II malformation, endocrine abnormalities, tethered cord, syringomyelia, and syringobulbia) or may be sequelae of the neurologic deficit (e.g., deformations of the limbs and spine; bladder, bowel, and sexual dysfunction; and learning disabilities).

In addition to the emotional cost of spina bifida, the estimated monetary cost is staggering. In the United States alone, the total cost of spina bifida over a lifetime (the direct costs of medical, developmental, and educational services and the indirect costs associated with morbidity and mortality, in 1992 dollars) for affected infants born in 1988 was almost $500 million, or $294,000 for each infant.

**TREATMENT**

Damage to open neural tissues appears to be progressive and results from exposure to toxic substances in the amniotic fluid and trauma to the neural tissue through contact with the uterine wall and birth canal. Although several studies have attempted to determine whether delivery by elective cesarean section before labor decreases the severity of motor impairment among infants with spina bifida, a recent review concluded that there is insufficient clinical evidence to determine whether such procedures provide substantial benefits and underscored the need for prospective, controlled data. In an effort to intervene even earlier, physicians have attempted to treat spina bifida surgically in utero as early as 22 weeks of gestation. Similar procedures performed on animal models with surgically created spina bifida, including sheep fetuses, resulted in near-normal neuro-

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**Figure 2. Lateral View of the Spinal Cord in Three Types of Spina Bifida.**

Spina bifida occulta occurs most often at S1, S2, or both and is a bony defect of the spine, usually covered by normal skin. A meningocele is a saccular herniation of meninges and cerebrospinal fluid through a bony defect of the spine. Meningoceles are usually covered by normal skin. A myelomeningocele is the most common type of spina bifida and is characterized by herniation of the spinal cord, nerves, or both through a bony defect of the spine. Myelomeningoceles are usually open defects in which either meninges or neural tissue is exposed to the environment. Of these three types, only meningocele and myelomeningocele are typically included in studies of spina bifida and are often jointly referred to as spina bifida cystica. The spinal cord and nerves are depicted in yellow and the cerebrospinal fluid is in black.
logic function among the animals that survived.\textsuperscript{32,36} However, current data are insufficient to assess the long-term neurologic benefit of this type of inter- 
vention or the risks of maternal and fetal morbidity. The observation that some components of the Ar- 
old–Chiari type II malformation resolved in some 
infants after in utero surgery\textsuperscript{34,37} is potentially 
important, since such malformations are a common cause of hydrocephalus and, later, neurologic deterioration in people with spina bifida.

Although innovative approaches are being tried at 
or before birth to limit the neurologic sequelae of 
spina bifida, medical care for people who are born 
with the disorder remains complex and challenging.\textsuperscript{38} In 1996, a study of secondary health conditions 
among adults with spina bifida showed that 47 per-
cent of hospital admissions over a 10-year period were 
due to secondary conditions, including urinary tract 
infections, calculi, and skin ulcerations, that were po-
tentially preventable.\textsuperscript{39} The dissemination of simple 
prevention techniques, such as regularly and com-
pletely eliminating urine from the bladder and avoid-
ing friction-causing movements, may be hampered 
by barriers such as lack of access to care, financial 
constraints, or lack of comprehensive treatment fa-

cilities with knowledgeable care givers for adults with 
spina bifida.\textsuperscript{39}

Latex allergy is another frequent and potentially 
preventable complication, reported in a recent study 
to affect 43 percent of people with spina bifida,\textsuperscript{40} but 
its occurrence may be reduced by avoiding the use 
of latex-containing products during the care of in-
fants and children with spina bifida.\textsuperscript{31} Children with 
spina bifida also do not grow at a normal rate. Growth 
hormone treatment has been reported to improve 
the growth of some children significantly, but results 
of studies of the long-term effects of such treatment 
are not yet available.\textsuperscript{52}

Despite the progress made in preventing second-
ary disabilities, however, these interventions will not 
 alleviate all the problems resulting from the failure 
of the neural tube to close properly. Therefore, pri-
mary prevention offers great potential for reducing 
the multiple burdens of illness and disability associ-
ated with spina bifida and other neural-tube defects.

**GENETIC AND ENVIRONMENTAL CAUSES**

Over the years, epidemiologic studies have been 
instrumental in elucidating the causes of neural-tube 
defects in humans. Overall, these studies have sug-
gested that environmental and genetic factors have a 
joint role in the causation of neural-tube defects. For 
example, they have revealed marked geographic and 
temporal variability in the rate of occurrence of these 
conditions as well as their association with race or 
ethnic background and socioeconomic status. Geo-
graphic variations, first observed decades ago among 
and sometimes within countries,\textsuperscript{43} are still reported 
today\textsuperscript{44,45} (Fig. 3); they may reflect joint contributions of environmental and genetic factors to the occurrence of neural-tube defects. In contrast, repeated 

reports of temporal trends, from seasonal variations\textsuperscript{46} to long-term trends over time,\textsuperscript{45,47} suggest the impor-
tance of environmental contributions, since gene fre-

quencies take generations to change appreciably. Ob-

servations of epidemics of neural-tube defects, which 
lasted a few years and are still largely unexplained,\textsuperscript{47} further add to the evidence in support of environ-
mental causes.

Variation in rates as a function of ethnic and racial 
background\textsuperscript{44,45,48,49} requires a more complex inter-

pretation. In the United States, higher rates of neu-
ral-tube defects have been observed among Hispan-
ics and non-Hispanic whites than among blacks.\textsuperscript{48,49} Some of these findings, however, tend to change over 
time\textsuperscript{49} or in response to changes in residence as a re-

sult of migration,\textsuperscript{48} suggesting that there are interac-

tions between ethnic background and environmen-
tal factors. Socioeconomic conditions have long been 
thought to contribute to the risk of neural-tube de-
fects, and rates of anencephaly and spina bifida are 
usually higher in groups with lower socioeconomic 
status.\textsuperscript{50} This association persists even after adjust-
ment for multivitamin use.\textsuperscript{51}

Identifying specific causal factors that can account 
for these general findings, however, has proved dif-
ficult. To date, few specific environmental causes of 
n neural-tube defects have been recognized, except for 
relatively rare sources of exposure, such as maternal 
diabetes\textsuperscript{52,53} and maternal use of some antiepileptic 


drugs, such as valproic acid.\textsuperscript{54} Other factors, including 
fever and hyperthermia in early pregnancy\textsuperscript{55,56} and 

obesity,\textsuperscript{57,60} have been proposed. To what extent oc-

upational or residential exposure may cause neural-
tube defects is still unclear.\textsuperscript{50} Identification of biologic 

markers for the direct measurement of exposure and 
effects in the mother and fetus will probably lead to 
critical insights.

By the mid-1970s, epidemiologic evidence sug-
gested that broadly defined environmental factors, 
interacting with genetic factors, had an important 
role in causing neural-tube defects. Because of marked 
changes in incidence in many areas of the world, it 
was clear that some important factor must have af-
fected large segments of the population. The in-
creased risk of neural-tube defects among people in 
lower socioeconomic groups has offered a clue to 
the factors that make poor families different from 
affluent families. Poor nutrition was an obvious can-
didate: nutrition can vary greatly over time and 
among countries, cultures, and social classes and may 
interact with a person’s genetic makeup. Further-
more, the effect of poor nutrition may be magnified 
in the developing embryo, where active cell prolif-
eration occurs at a time when access to nutrients is 
limited.
Micronutrients

In 1976, Smithells and colleagues in Britain reported that women who gave birth to babies with neural-tube defects had low serum levels of micronutrients, including some vitamins.62 These findings led them to propose a randomized, controlled trial of vitamin supplementation. However, because of ethical considerations, they were permitted by their institution to undertake only a nonrandomized intervention, in which they offered a multivitamin containing 360 µg of folic acid to women who planned to become pregnant and who had previously had a fetus or infant with a neural-tube defect.63 In 1983, they reported that among women who had previously had an affected pregnancy, those who took the multivitamin during the early stages of pregnancy had an 86 percent lower risk of having another affected fetus or infant than those who did not take the multivitamin.63 However, because Smithells and colleagues had not been permitted to randomly assign the use of the multivitamin among participants in their study, their finding did not lead to any public health action. No such action was initiated until the publication of the results of two randomized studies a decade later.

In 1991, the results of a trial sponsored by the British Medical Research Council indicated that the risk of recurrent neural-tube defects was significantly lower among women who took 4000 µg of folic acid daily (without other vitamins) than among those who did not,3 and in 1992, a Hungarian study reported that women who took a multivitamin containing 800 µg of folic acid had a significantly lower risk of a first occurrence of a neural-tube defect in a fetus or infant than women who did not.4 These results were supported by the collective findings of observational studies64-69 and a small, inconclusive, randomized trial70 that examined the association between the use of multivitamin or folic acid supplements and the risk of

Figure 3. International Variation in the Rates of Spina Bifida and Anencephaly.

Birth rates include (where available) cases reported in pregnancy terminations and are based on data from birth-defects registries that, as a rule, monitor only part of a country’s population of newborns. Data are shown for the following countries (and cities or area registries): the United States (Atlanta and Hawaii), Australia (Victoria and South Australia), the United Kingdom (Glasgow and North Thames registry), Spain (Basque provinces), Norway, France (Paris, Strasbourg, and Bouches-du-Rhône and Central East France registry), Ireland and Northern Ireland (Dublin and Belfast), the Czech Republic, Belgium (Hainaut and Namur), Italy (Campania, Emilia–Romagna, and Tuscany), the Netherlands (northern), Denmark (Odense), Switzerland (selected counties), and northern and southern China13 (selected counties). Rates for Mexico, the South American countries, and Japan were estimated from hospital-based registries. Except as noted, data for all areas are those published by the International Center for Birth Defects44 and the European Registration of Congenital Anomalies.
neural-tube defects (Fig. 4). Most recently, in a community-based intervention study, Berry et al. documented the effectiveness of a daily dose of 400 µg of folic acid alone in preventing neural-tube defects in an area of China with a high incidence of such defects and one with a low incidence.

Genes and Genetic and Environmental Interactions

The findings of the British and Hungarian clinical trials generated much research on folate metabolism in an effort to identify the genetic and biochemical bases of neural-tube defects. Together with numerous other enzymes and cofactors, folate is involved in single-carbon transfers that are an integral part of many processes, including the synthesis of nucleotides and a variety of methylation reactions that occur in several cell compartments (e.g., the cytosol, nucleus, and mitochondria). After it was reported that some women who had previously had an affected fetus or infant had increased blood levels of homocysteine, research centered mostly on the metabolic cycle in which homocysteine undergoes remethylation to methionine (Fig. 5). Several genes were studied, including those encoding folate receptors, 5,10-methylenetetrahydrofolate reductase (MTHFR), cystathionine β-synthase, methionine synthase, methionine synthase reductase, and methylenetetrahydrofolate dehydrogenase, a trifunctional enzyme.

Although much remains to be learned, initial findings indicate that the genetic contribution to neural-tube defects is likely to be complex. For example, an approximate doubling of the risk of spina bifida has been associated with homozgyosity for a common mutation in the gene for MTHFR, the C677T allelic variant, which encodes an enzyme with reduced activity. Furthermore, the frequency of the allele in certain ethnic groups roughly correlates with the incidence of neural-tube defects: it is common among Hispanics, less common among non-Hispanic whites, and relatively rare in blacks. Other factors must be involved, however, since the correlation is far from perfect. For example, in Italy, the C677T variant is common, but the rate of occurrence of neural-tube defects is low. Moreover, even if the association were causal, this MTHFR variant would account for only a small fraction of the cases of neural-tube defects prevented by folic acid. Indeed, several studies suggest that complex interactions may occur among genes, between alleles of the same gene, and between certain genotypes and...
environmental factors. For example, the risk of neural-tube defects might vary if mutations in the gene encoding MTHFR occurred with mutations in other folate-related genes or if two different mutations in the MTHFR gene occurred together. Some studies also suggest that the risk associated with certain genotypes may vary depending on maternal factors, such as the blood levels of vitamin B12 or folate. In addition, in some cases the risk may be offset by an intervention such as the use of vitamin supplements. Intriguing as they are, many of these findings still await confirmation and warrant further investigation. Other possibilities are suggested by studies in which certain animal models were found to be sensitive to other micronutrients in addition to folate. A global interpretation of these findings is certainly premature. Nevertheless, their consistency with the complex etiology of neural-tube defects, as revealed by epidemiologic and clinical studies, is remarkable.

**PRIMARY PREVENTION**

The link between nutrition and the occurrence of neural-tube defects provides a powerful tool for primary prevention. After the release of the two randomized studies described above, the Public Health Service recommended in 1992 that women capable of becoming pregnant should consume 400 µg of folic acid per day. Because as many as 50 percent of pregnancies in the United States are unplanned and because the neural tube develops before most women know they are pregnant, it was also recommended that women consume this amount of folic acid routinely. In other countries, such as Australia and the Netherlands, public health advisories suggested that women plan and prepare for their pregnancies and that they consume 400 µg of folic acid daily while they are attempting to become pregnant and during early pregnancy.

The Public Health Service suggested that the desired level of consumption of folic acid could be achieved by taking dietary supplements containing folic acid, by increasing consumption of foods rich in naturally occurring folate compounds (compounds that have the nutritional properties of the synthetic folic acid used in supplements), and by consuming foods fortified with folic acid (Table 1). Dietary supplements containing 400 µg of folic acid are readily available in the United States, most commonly as multivitamins and less often as folic acid alone. A few breakfast cereals contain 400 µg of folic acid per serving, and many contain 100 µg. Consuming foods rich in naturally occurring folate compounds, such as fruits and vegetables, would provide variable amounts of

![Diagram of the Metabolic Roles of Folic Acid](image-url)
TABLE 1. WAYS OF INCREASING WOMEN’S FOLIC ACID INTAKE AND BLOOD FOLATE LEVELS TO PREVENT NEURAL-TUBE DEFECTS.

<table>
<thead>
<tr>
<th>APPRAOCH</th>
<th>ADVANTAGES</th>
<th>CHALLENGES</th>
<th>STATUS IN THE UNITED STATES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortification of staple foods</td>
<td>Proved to increase blood folate levels</td>
<td>Current fortification adds only one-fourth the recommended amount to the daily diet</td>
<td>Implemented in January 1998</td>
</tr>
<tr>
<td></td>
<td>Available to almost all women</td>
<td>Sustained change in behavior required for consumption of higher amounts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inexpensive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased intake of supplements</td>
<td>Efficacy proved in clinical trials</td>
<td>Sustained change in behavior required</td>
<td>About 30% of women of reproductive age now take supplements</td>
</tr>
<tr>
<td></td>
<td>Proved to increase blood folate levels</td>
<td>Cooperation of medical and nutritional professionals required</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relatively inexpensive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased consumption of foods with high levels of natural folates</td>
<td>Other benefits of a varied diet that includes fruits and vegetables</td>
<td>Efficacy not proved</td>
<td>Campaign for “five-a-day” consumption of fruits and vegetables under way*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increases blood folate levels much less than supplements or fortified foods</td>
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<tr>
<td></td>
<td></td>
<td>Sustained change in behavior required</td>
<td></td>
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<td></td>
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<td>Expensive</td>
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*This is a campaign sponsored by the National Cancer Institute and the Produce for Better Health Foundation.

folate, in addition to the other benefits of a varied diet. After a landmark public health decision by the Food and Drug Administration,6 all enriched grain products, such as flours and pastas, in the United States are now also fortified with 140 µg of folic acid per 100 g of grain. In 1997, it was estimated that the average American woman of reproductive age would consume about 100 µg of folic acid per day from foods containing enriched grain products.7

In practice, however, the effectiveness of supplements, a varied diet, and fortified foods in providing women with the benefits of the recommended daily dose of 400 µg of folic acid may vary (Table 1). Supplements are readily available, provide a convenient way for many women to ensure that they get enough folic acid, and have proved effective in clinical trials. Breakfast cereals, too, are readily available and convenient. The ability of foods naturally rich in folate to provide consistently the same benefits as folic acid supplements is less clear and has not been tested in clinical trials. Naturally occurring folate is less readily absorbed than synthetic folic acid in supplements or cereals,8 prompting the Institute of Medicine in 1998 to recommend that women of childbearing age obtain 400 µg of folic acid daily from dietary supplements or fortified foods.7 Finally, fortification appears to have increased the intake of folic acid in the general population, although at the current level of fortification only a few women may receive the recommended dose by this route alone.89,90

Cereal grains are not fortified with a higher level of folic acid because of concern that greater consumption of folic acid might delay the diagnosis of vitamin B₁₂ deficiency in some cases. This concern led the Public Health Service in 1992 to recommend that daily consumption of folate from all sources not exceed 1000 µg per day.4 The 1998 report of the Institute of Medicine suggested that the upper limit of consumption of synthetic folic acid be 1000 µg, regardless of the amount of naturally occurring folates in the diet.7 Had the Institute of Medicine guidelines been available earlier, flour might have been fortified at a higher level. In a trial in which women were randomly assigned to receive one of four interventions (folic acid supplements, foods fortified with folic acid, foods naturally rich in folates, or dietary advice) or to a control group, women who consumed 400 µg of folic acid daily by taking supplements or eating fortified foods had increases of 40 to 50 percent over base-line values in their red-cell folate levels, as compared with an 11 percent increase among those who consumed 400 µg of natural folate daily from foods and a 5 percent increase in the control group.91

Regardless of the method chosen to increase folic acid intake, the full potential of this vitamin for preventing neural-tube defects will be realized only if women who might become pregnant change their habits substantially. If the rate of unplanned pregnancies in the United States88 were lower, a more focused approach, such as periconceptional intake of folic acid (currently being tried in the Netherlands92,93), might work. A national survey conducted in the United States in 1998 found that about one third of women of childbearing age now take a vitamin supplement containing 400 µg of folic acid daily, although most were not aware that doing so would lower their risk of having a fetus or child with a neural-tube defect.94 Of the women who had heard about folic acid, only 19 percent had obtained that information from health care providers.94 Physicians and other health care providers have a potentially important part...
to play in disseminating information about folic acid. To that end, a number of professional organizations recently formed the National Council on Folic Acid in order to increase public and professional awareness of the potential benefits of increased folic acid consumption.

NEW CHALLENGES AND PERSPECTIVES

Progress in the clinical treatment of neural-tube defects, research on pathogenesis, and approaches to primary prevention open new avenues and pose considerable challenges. Although in the United States more than 90 percent of infants with spina bifida live for more than a year, many continue to have progressive deterioration because of a variety of medical complications. Well-conducted intervention studies will be instrumental in solving controversies about treatment and achieving optimal care. Likewise, clarification of the therapeutic value of in utero surgery and the use of cesarean section before labor for improving the long-term outcome of people with spina bifida awaits further data.

The genetic and environmental causes of neural-tube defects also remain to be fully determined. At least 30 percent of neural-tube defects are not prevented by the consumption of folic acid supplements and not all epidemiologic findings can readily be explained. In addition, the potential of folic acid and, to a greater extent, of other micronutrients to prevent neural-tube defects remains to be explored. For example, we do not know what the optimal daily dose of folic acid is or whether some women who do not benefit from 400 µg daily would benefit from higher doses. Selecting a target level of intake that is appropriate for an entire population is a complex decision. Whereas some findings have suggested that an average daily intake of less than 400 µg might prevent some cases of neural-tube defects, the same data also suggest that an intake of 400 µg would prevent considerably more cases.

The evolving knowledge derived from studies of neural-tube defects also raises some general issues. For example, traditional benchmarks of adequate micronutrient intake, such as prevention of macrocytic anemia in the case of folic acid, may need to be re-evaluated to encompass additional health benefits (such as the prevention of neural-tube defects) or their biochemical correlates. The worldwide contributions to randomized trials and intervention trials highlight the value of international collaboration in solving issues that ultimately are global. Finally, research into the prevention of neural-tube defects may reap unexpected benefits if it is confirmed that the risks of other birth defects, such as some congenital anomalies of the heart, face, limbs, and urinary tract, might also be reduced by vitamin use.

Today, the urgent challenge facing medical and public health professionals with respect to neural-tube defects is how to translate our knowledge about primary prevention into practice. Every day, affected infants are born, and women with affected fetuses electively terminate their pregnancies. In the United States, options for prevention include increasing the level of fortification of grains, increasing the consumption of foods now fortified with folic acid, and increasing the consumption of vitamin supplements containing folic acid. Improving the knowledge and changing the habits of women and medical professionals will be critical in efforts to realize the full preventive potential of folic acid. The global health community must make a concerted effort to meet this challenge.

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