Review Articles

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 States[1] 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 States[6] and despite recommendations by the Institute of Medicine[7] and the Public Health Service[8] 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 models[9,10] and prenatal diagnosis[11] are beyond the scope of this article.

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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 bifida[12] (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

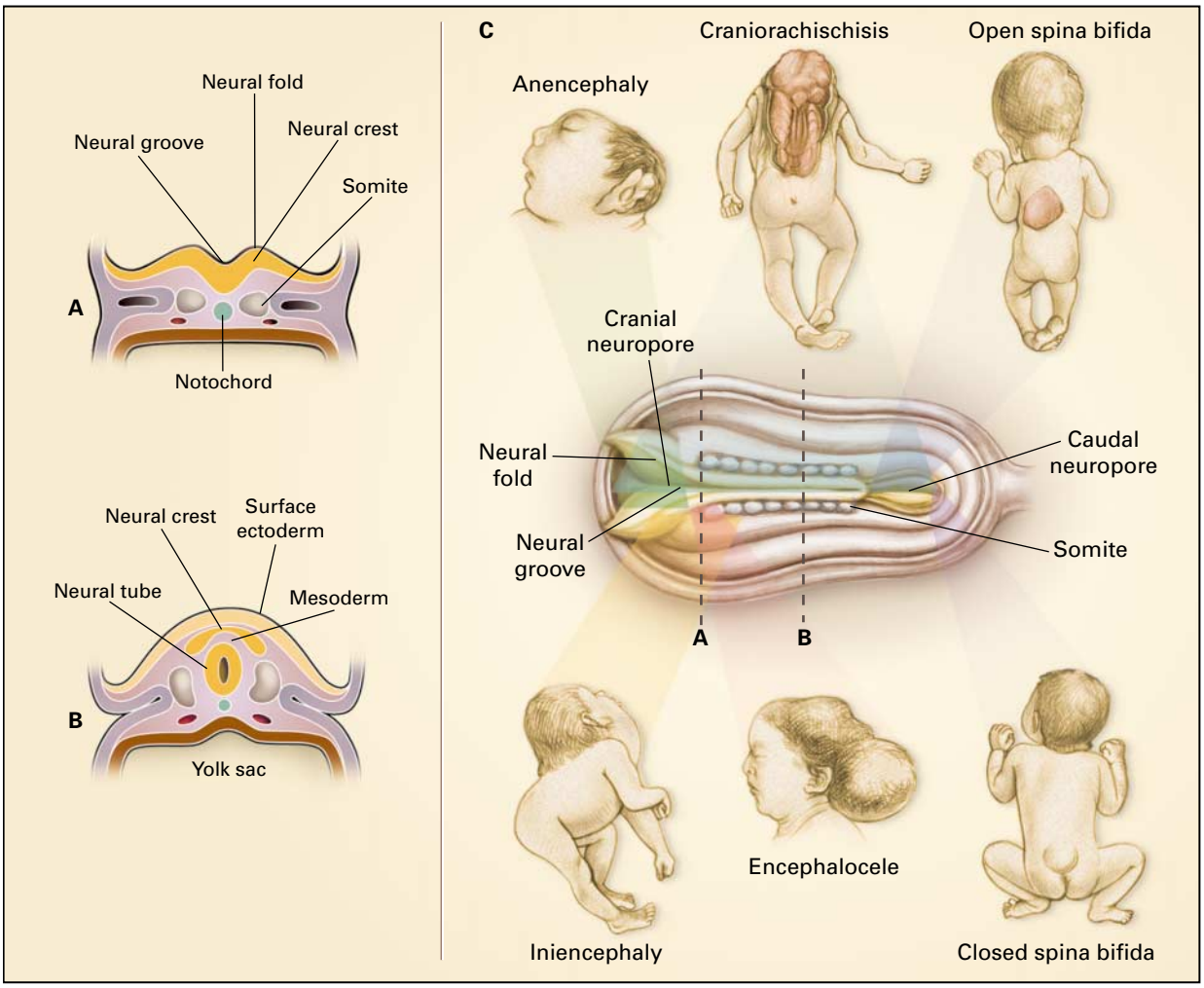

Figure 1. Features of Neural-Tube Development and Neural-Tube Defects.

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.

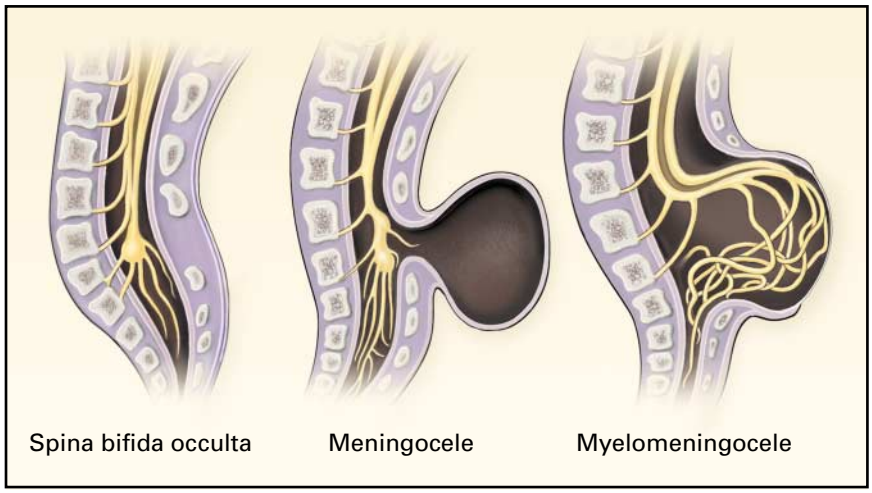

Figure 2. Lateral View of the Spinal Cord in Three Types of Spina Bifida.

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.

spontaneous or elective abortion.[1,8] 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,[13] whereas in the Netherlands it is 35 percent[24] and in the United States it is 10 percent.[25] 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.[25,26]

Infants with spina bifida who survive are likely to have severe, life-long disabilities[27] and are at risk for psychosocial maladjustment.[28] 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.[29]

TREATMENT

Damage to open neural tissues appears to be progressive and results from exposure to toxic substances in the amniotic fluid[30] and trauma to the neural tissue through contact with the uterine wall and birth canal.[31] 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[32] 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.[33-35] Similar procedures performed on animal models with surgically created spina bifida, including sheep fetuses, resulted in near-normal neuro-

logic function among the animals that survived.[33,36] However, current data are insufficient to assess the long-term neurologic benefit of this type of intervention or the risks of maternal and fetal morbidity. The observation that some components of the Arnold–Chiari type II malformation resolved in some infants after in utero surgery[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.[38] In 1996, a study of secondary health conditions among adults with spina bifida showed that 47 percent of hospital admissions over a 10-year period were due to secondary conditions, including urinary tract infections, calculi, and skin ulcerations, that were potentially preventable.[39] The dissemination of simple prevention techniques, such as regularly and completely eliminating urine from the bladder and avoiding friction-causing movements, may be hampered by barriers such as lack of access to care, financial constraints, or lack of comprehensive treatment facilities with knowledgeable care givers for adults with spina bifida.[39]

Latex allergy is another frequent and potentially preventable complication, reported in a recent study to affect 43 percent of people with spina bifida,[40] but its occurrence may be reduced by avoiding the use of latex-containing products during the care of infants and children with spina bifida.[41] 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.[42]

Despite the progress made in preventing secondary disabilities, however, these interventions will not alleviate all the problems resulting from the failure of the neural tube to close properly. Therefore, primary prevention offers great potential for reducing the multiple burdens of illness and disability associated 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 suggested 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. Geographic variations, first observed decades ago among and sometimes within countries,[43] are still reported today[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[46] to long-term trends over time,[45,47] suggest the importance of environmental contributions, since gene frequencies take generations to change appreciably. Observations of epidemics of neural-tube defects, which lasted a few years and are still largely unexplained,[47] further add to the evidence in support of environmental causes.

Variation in rates as a function of ethnic and racial background[44,45,48,49] requires a more complex interpretation. In the United States, higher rates of neural-tube defects have been observed among Hispanics and non-Hispanic whites than among blacks.[48,49] Some of these findings, however, tend to change over time[49] or in response to changes in residence as a result of migration,[48] suggesting that there are interactions between ethnic background and environmental factors. Socioeconomic conditions have long been thought to contribute to the risk of neural-tube defects, and rates of anencephaly and spina bifida are usually higher in groups with lower socioeconomic status.[50] This association persists even after adjustment for multivitamin use.[51]

Identifying specific causal factors that can account for these general findings, however, has proved difficult. To date, few specific environmental causes of neural-tube defects have been recognized, except for relatively rare sources of exposure, such as maternal diabetes[52,53] and maternal use of some antiepileptic drugs, such as valproic acid.[54] Other factors, including fever and hyperthermia in early pregnancy[55,56] and obesity,[57-60] have been proposed. To what extent occupational or residential exposure may cause neural-tube defects is still unclear.[61] 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 suggested 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 affected large segments of the population. The increased 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 candidate: nutrition can vary greatly over time and among countries, cultures, and social classes and may interact with a person's genetic makeup. Furthermore, the effect of poor nutrition may be magnified in the developing embryo, where active cell proliferation occurs at a time when access to nutrients is limited.

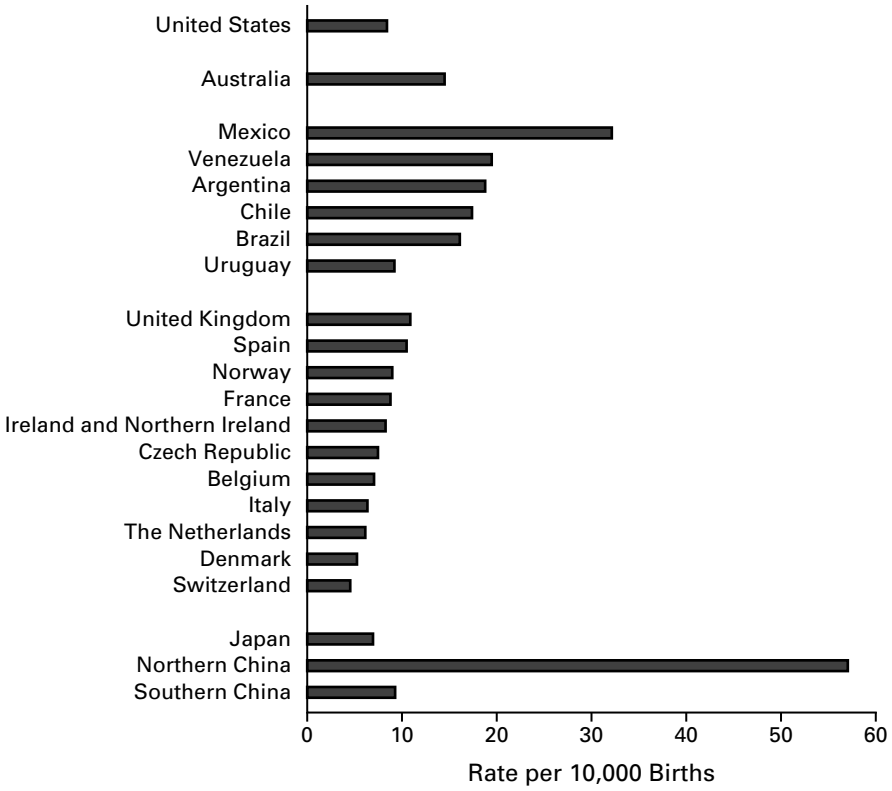

Figure 3. International Variation in the Rates of Spina Bifida and Anencephaly.

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[13] 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-Rhone 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 China[13] (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 Defects[44] and the European Registration of Congenital Anomalies.

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 studies[64-69] and a small, inconclusive, randomized trial[70] that examined the association between the use of multivitamin or folic acid supplements and the risk of

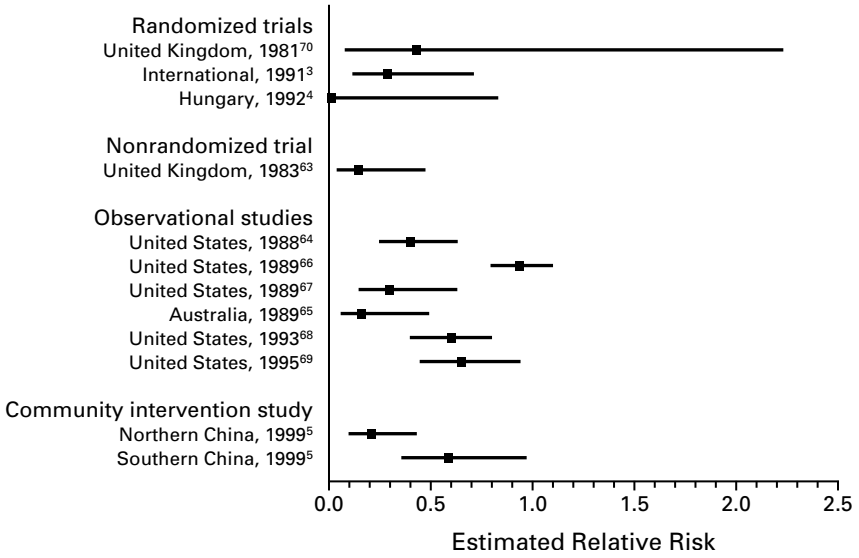

Figure 4. Summary of Studies of the Risk of Neural-Tube Defects and the Use of Folic Acid or Multivitamin Supplements, 1981 through 1999.

Two randomized, controlled trials[3,70] and one nonrandomized trial[63] examined the efficacy of folic acid alone[3] or with other vitamins[3,63,70] among women who had previously had an affected fetus or infant. One randomized trial assessed the efficacy of a multivitamin containing folic acid among women who had not had an affected fetus or infant.[4] Of the observational studies, five[64-66,68,69] were case–control studies, whereas one[67] was an observational cohort study. One community-based intervention study[5] assessed the effectiveness of folic acid supplements alone among women who had not had an affected fetus or infant in an area of northern China that had a high rate of neural-tube defects and an area in southern China that had a low rate. The values shown are the relative risks of a neural-tube defect among the fetuses or infants of women who took folic acid as compared with those of women who did not take folic acid. Bars indicate 95 percent confidence intervals.

neural-tube defects (Fig. 4). Most recently, in a community-based intervention study, Berry et al.[5] 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[3,4] 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).[71] After it was reported that some women who had previously had an affected fetus or infant had increased blood levels of homocysteine,[72,73] 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 homozygosity for a common mutation in the gene for MTHFR, the C677T allelic variant,[74] which encodes an enzyme with reduced activity.[75] 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.[74] 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.[74] 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.[74]

Indeed, several studies suggest that complex interactions may occur among genes, between alleles of the same gene, and between certain genotypes and

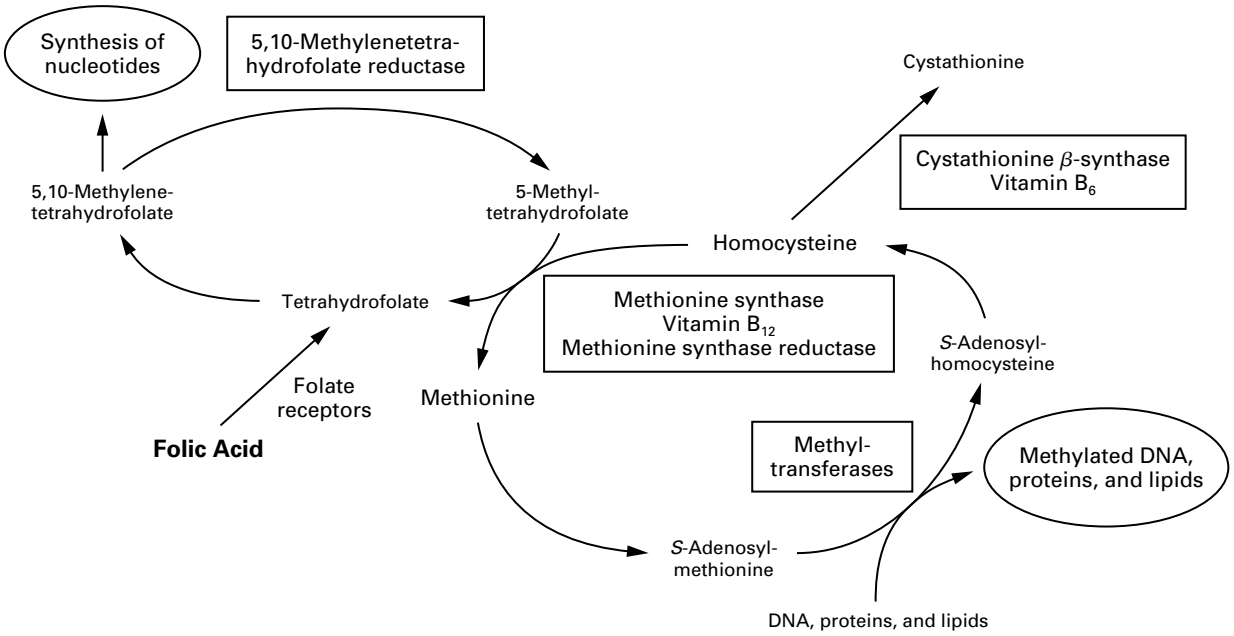

Figure 5. The Metabolic Roles of Folic Acid.

After entering the cell, folic acid, possibly with the aid of folate receptors, is involved in the transfer of carbon atoms that are used to synthesize nucleotides or, through the conversion of homocysteine to methionine, for the methylation of a variety of substrates. These processes are regulated by numerous molecules, including enzymes and vitamins other than folic acid (e.g., vitamins B_6 and B_{12}). The activity of some enzymes, such as methionine synthase, may be influenced by other enzymes, such as methionine synthase reductase. Enzymes and factors that may be important in neural-tube development are indicated by boxes.

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[76-78] or if two different mutations in the MTHFR gene occurred together.[79,80] Some studies also suggest that the risk associated with certain genotypes may vary depending on maternal factors, such as the blood levels of vitamin B_{12}[81] or folate.[82] In addition, in some cases the risk may be offset by an intervention such as the use of vitamin supplements.[83,84] 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.[9,10] 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,[3,4] the Public Health Service recommended in 1992 that women capable of becoming pregnant should consume 400 μg of folic acid per day.[8] Because as many as 50 percent of pregnancies in the United States are unplanned[85] 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.[86]

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[8] (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

TABLE 1. WAYS OF INCREASING WOMEN'S FOLIC ACID INTAKE AND BLOOD FOLATE LEVELS TO PREVENT NEURAL-TUBE DEFECTS.

APPROACH	ADVANTAGES	CHALLENGES	STATUS IN THE UNITED STATES
Fortification of staple foods	Proved to increase blood folate levels Available to almost all women Inexpensive	Current fortification adds only one-fourth the recommended amount to the daily diet Sustained change in behavior required for consumption of higher amounts	Implemented in January 1998
Increased intake of supplements	Efficacy proved in clinical trials Proved to increase blood folate levels Relatively inexpensive	Sustained change in behavior required Cooperation of medical and nutritional professionals required	About 30% of women of reproductive age now take supplements
Increased consumption of foods with high levels of natural folates	Other benefits of a varied diet that includes fruits and vegetables	Efficacy not proved Increases blood folate levels much less than supplements or fortified foods Sustained change in behavior required Expensive	Campaign for "five-a-day" consumption of fruits and vegetables under way*

*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.[87]

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,[88] 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 B_{12} 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.[8] 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 States[85] were lower, a more focused approach, such as periconceptional intake of folic acid (currently being tried in the Netherlands[92,93]), might work. A national survey conducted in the United States in 1998 found that about one third of women of childbearing age 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.[26] Well-conducted intervention studies will be instrumental in solving controversies about treatment and achieving optimal care.[95] 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[96,97] 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,[98] the same data also suggest that an intake of 400 μg would prevent considerably more cases.[99]

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 reevaluated to encompass additional health benefits (such as the prevention of neural-tube defects) or their biochemical correlates. The worldwide contributions to randomized[3,4] and intervention[5] 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.[100]

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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