Neural tube defects (NTD) are one of the most disabling congenital defects in the human. NTD applies to malformation of the brain and/or spinal cord. The process of the formation of the nervous system is called neurulation. During neurulation, the flat neural plate transforms into a cylindrical neural tube with canalization and rostral and caudal closure. When the closure does not occur at the rostral end, the brain does not develop. This defect is clinically recognized as anencephaly.

When caudal closure does not occur, spina bifida will be the end result. Spina bifida can result in paralysis of the legs, the bladder, the rectum, and hydrocephalus.

This closure process of the neural tube occurs very early in human pregnancy: from d 21 until d 28 after conception or 1 wk after the expected menstruation. This illustrates the fact that any measure of prevention has to start before conception.

NTD as a Result of Genetic and Environmental Factors

The birth prevalence of NTD depends on the country and socioeconomic and ethnic groups. The numbers range from 1:2500 in Finland, 1:300 in Mexico, to 1:80 in South Wales.

Neural tube formation as well as NTD are guided or caused by a multifactorial process, involving both genetic and environmental factors. Recognized genetic factors are sex differences, ethnic differences, consanguinity, increased rate of concordance in monozygotic twins, increased prevalence in siblings and in children of affected patients, single-gene mutation and chromosomal abnormalities. Suggested environmental influences are nutri-
tion, diabetes, hyperthermia, teratogens like aminopterin, thalidomide, valproic acid, and other antiepileptics, alcohol, or profession.

NTD AND NUTRITION

Numerous reports have suggested that nutritional deficiencies in general would cause adverse birth outcomes. As an example, a Dutch midwife found an increase in NTD in 1722 and 1732, 2 yr that were linked with poor crops. She also noted that the children with NTD came from the poorest homes in urban areas (1). A similar observation was made in the children who were exposed in utero to severe food shortage during the Second World War in Holland. In addition to a significant decrease in birth weight, there was also a significant increase in the rate of NTD (2).

NTD AND FOLATES

The possibility that folate was specifically linked to NTD in humans was first reported by Hibbard (3). Using the FIGLU test, he observed that women who had pregnancies associated with fetal malformations had a higher incidence of aberrant folate metabolism. Hibbard and Smithells (4) subsequently repeated this finding. Also, a key role of folate in preventing NTD was suggested.

Folate status is now assessed by the determination of folate in serum/plasma and red blood cells. Folate can be determined with a microbiological assay with an interassay and intraassay variation of less than 5% (O’Brien and Keller 1992). In more recent reports, the radioassay technique is used with a variation coefficient of less than 10%. The concentration of folates in red blood cells is considered to represent the body storage over the last 7 wk, especially in the liver (Herbert 1990). In most studies, the method of determination of folate and the intraassay and interassay variation coefficient is not mentioned.

It is striking that in all studies in pregnant women who received no vitamin supplementation, a strong decrease of maternal folate serum or plasma levels during the course of pregnancy were reported. Therefore, studies on folate status in women in relation to NTD have to take into account the existence of pregnancy or not.

Studies on blood folate and red cell folate levels in nonpregnant women with NTD offspring did not show significant differences with controls (5–8). This implies that folate values are not predictive for NTD.

Maternal folic acid levels studies in the first trimester of pregnancy in mothers with NTD offspring tended to be lower than in controls (Tables 1