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Chapter 61

# The neurology of folic acid deficiency

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## HISTORICAL BACKGROUND

Any modern understanding of the relationship of folic acid to nervous system disorders requires some consideration of the historical evolution of our concepts of the neurology of both folic acid and vitamin $B_{12}$ deficiency. This is necessary because of (1) the intimate relationship between folic acid and vitamin $B_{12}$ metabolism; (2) the morphologically indistinguishable megaloblastic anemias that can be caused by either deficiency state; (3) the overlapping neuropsychiatric syndromes and neuropathology associated with either deficiency or related inborn errors of metabolism.

In the late 19th century, the earliest accounts of the neurologic associations of megaloblastic anemia were by Leichtenstern (1884) ("Progressive pernicious anemia in tabetic patients") and Lichtheim (1887), who described typical lesions in the posterior and lateral columns of the spinal cord, for which Russell et al. (1900) coined the term "subacute combined degeneration of the cord" (SCD) when they reported the first full account of the disorder.

In the first third of the 20th century, before treatment became available in the form of liver extract, the neuropsychiatry and neuropathology of megaloblastic anemia was thoroughly documented by many authors (Woltmann, 1919; Ahrens, 1932; Kinnier Wilson, 1940). They recognized: (1) that the nervous system complications could be very varied and included peripheral nerve and psychiatric disorders as well as the classic cord syndrome (SCD); (2) there was often considerable dissociation between the hematologic and neuropsychiatric manifestations, either of which could precede the other. In the absence of treatment, however, patients with megaloblastic anemia would eventually almost all develop some nervous system involvement before death. At this time before the discovery of folic acid or vitamin $B_{12}$ the separation of megaloblastic anemias had not begun and most were regarded as "pernicious anemia," which rested on the demonstration of achlorhydria. Kinnier Wilson (1940) noted that in neurologic series acid was found in the stomach in up to 25%.

Unfortunately folic acid was synthesized first in 1945, 3 years ahead of the isolation of vitamin $B_{12}$, and was immediately utilized in the treatment of "pernicious anemia" as the possibly deficient dietary factor (Chanarin, 1969). These trials were encouraged by some initially promising improvement in the megaloblastic anemia. However, over the subsequent 5 years and beyond there followed several disturbing reports of aggravation or precipitation of the neurologic complications of "pernicious anemia" by the vitamin (Hall and Watkins, 1947; Schwartz et al., 1950). In fact, folic acid was also often associated with later deterioration in the anemia after the initial improvement (Schwartz et al., 1950); and in some reports there was some temporary improvement in neurologic symptoms before the more florid deterioration (Hall and Watkins, 1947; Reynolds, 1976).

These developments in the period 1945–1950 had a profound effect on subsequent concepts. The introduction of vitamin $B_{12}$ treatment, with its beneficial effects on both the blood and the nervous system, coincided with the height of concern about folic acid. In the third quarter of the 20th century it was therefore erroneously assumed: (1) that the neuropsychiatry of megaloblastic anemia, so carefully documented in the preceding half century, was that of vitamin $B_{12}$ deficiency only; (2) that folic acid was only harmful to the nervous system and there was no neuropsychiatry of folic acid deficiency (see Reynolds, 1976, 1979a).

In the last third of the 20th century these deeply held misconceptions were slowly eroded with the application

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of folate and vitamin $B_{12}$ assays and other techniques to neuropsychiatric patients with and without megaloblastic anemia (Chanarin, 1969; Reynolds, 1976; Botez and Reynolds, 1979), reinforced later by the introduction of homocysteine assays in the 1990s (Carmel and Jacobsen, 2001). Such is the interest now in the role of folates, vitamin $B_{12}$, and homocysteine in brain metabolism and function at all ages, especially in relation to nervous system development, repair, mood, aging, cognitive function, and dementia (Massaro and Rogers, 2002; Reynolds, 2002a, 2006; Bottiglieri and Reynolds; 2010; Morris and Jacques, 2010), that some have questioned whether folic acid ever had any harmful effects on the nervous system (Dickinson, 1995), another misconception because the vitamin, as with almost all treatments, is associated with benefits and some risks (Reynolds, 2002b).

## FOLATE METABOLISM

Reviews of the structure, binding, absorption, transport, metabolism, and function of folates, including polymorphisms of folate-related enzymes and the interaction of folate and vitamin $B_{12}$ metabolism, are the subject of textbooks (Chanarin, 1969; Bailey, 1995, 2010).

Folic acid, also known as pteroyglutamic acid, consists of a pteridine ring linked to p-aminobenzoic acid, in turn linked to glutamic acid. Biologically active folates are reduced by the addition of two or four hydrogen atoms and are referred to as dihydro- or tetrahydrofolates. Some intracellular folate derivatives have additional glutamic acid residues attached to the terminal glutamic acid to produce so-called folylpolyglutamates.

Central to our understanding of folate metabolism is the folate cycle (Fig. 61.1) in which tetrahydrofolate (THF) accepts a single carbon unit from serine which is progressively reduced through formyl (CHO), methenyl ($CH^+$), and methylene ($CH_2$) derivatives, ultimately to 5-$CH_3$ tetrahydrofolate (5-MTHF). The latter gives up its methyl group to homocysteine to form methionine in an important enzymatic reaction mediated by methionine synthase and catalyzed by vitamin $B_{12}$, the key area of interaction between folate and vitamin $B_{12}$ metabolism (Fig. 61.1). The released THF begins the cycle of methyl group synthesis all over again. The methyl groups are passed on from methionine to *S*-adenosylmethionine (SAM), which is the major donor of methyl groups in innumerable genomic and nongenomic methylation reactions in all tissues, including the nervous system, involving nucleoproteins, proteins, lipids, monoamines, etc. SAM also exerts feedback control on methionine synthase activity (Fig. 61.1).

The interconversion of the various carbon-linked folate derivatives in the folate cycle also provides carbon units for other important metabolic pathways. In particular, 5,10-methylene-THF is essential for the synthesis of purines and pyrimidines and therefore ultimately for nucleotide, DNA, and RNA synthesis and, therefore, genetic function. Epigenetic function is in turn also linked to methylation reactions involving SAM.

The circulating form of folate monoglutamates in body fluids including serum and cerebrospinal fluid (CSF) is 5-methyltetrahydrofolate (5-MTHF). Remarkably, folate levels are two to three times higher in CSF than in serum and a high degree of correlation between the two exists in controls and in neurologic and psychiatric patients (Reynolds et al., 1972). An active transport process for 5-MTHF across the blood–brain barrier via the choroid plexus has been confirmed (Spector and Lorenzo, 1975). The correlation between serum

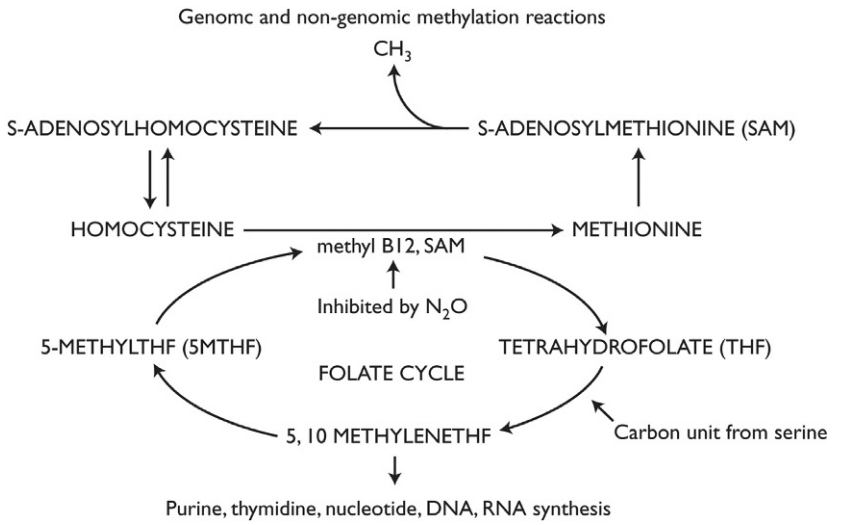


**Fig. 61.1.** Relationships between the folate cycle, vitamin $B_{12}$, methylation and nucleotide synthesis. SAM, *S*-adenosylmethionine; THF, tetrahydrofolate; $N_2O$, nitrous oxide.

and CSF folate is lost during clinical treatment with folic acid because the blood–brain barrier mechanism limits the entry of 5-MTHF, perhaps in part because of the convulsant properties of folate derivatives which have been demonstrated experimentally (Hommes et al., 1973; Reynolds, 1976).

Because mammalian cells are unable to synthesize folates *de novo* specialized carrier-mediated transport systems for the absorption and delivery of folate derivatives from food have been developed. The three main types of transport system are: the proton-coupled folate transporter (PCFT), the reduced folate carrier (RFC), and a small family of folate receptors (FRs), the latter encoded by three distinct genes i.e., FR$\alpha$, FR$\beta$ and FR$_\gamma$. Both FR$\alpha$ and RFC are involved in the transport process across the blood–brain barrier and into neuronal cells (Ramaekers et al., 2005; Wollack et al., 2008).

There has been increasing interest in the last decade in the role of genetic folate polymorphisms in human health, including vascular disease, cancer, and nervous system disorders, especially birth defects (Lucock, 2004; van der Linden et al., 2005; Christensen and Rozen, 2010). Particular attention has focused on MTHFR, especially the 677C→T variant, and methionine synthase, but no folate enzyme is exempt. Large-scale epidemiologic studies are required to clarify the health impact of these polymorphisms which may assume greater significance only if they are severe or if there are additional nutritional deficiencies and/or other genetic predispositions.

The metabolic basis of megaloblastic anemia has been thoroughly studied and is similar in both folic acid and vitamin $B_{12}$ deficiency (Stabler, 2010). The two basic mechanisms involve: (1) DNA synthesis, especially the impaired incorporation of thymidine and misincorporation of uracil into DNA; (2) methylation, especially impairment of SAM-dependent methylation of DNA (Fig. 61.1). The key metabolic reaction is the vitamin $B_{12}$-dependent methylation of homocysteine by methionine synthase to produce methionine. In folate deficiency there appears to be a failure in the supply of methyl groups. In vitamin $B_{12}$ deficiency there appears to be a block in the utilization of methyl groups. As will be discussed in this review, these mechanisms involving DNA synthesis and genomic and nongenomic methylation appear also to be at the heart of the neurologic manifestations of these deficiency states.

## THE NEUROLOGY OF FOLATE-DEFICIENT MEGALOBLASTIC ANEMIA

Our understanding of the neurology of folic acid or vitamin $B_{12}$ deficiency is greatly influenced by the many clinical and pathologic descriptions in the first half of the 20th century of patients with neuropsychiatric associations of megaloblastic anemia, who usually progressed to death from either the anemia or the neurologic complications in the era before treatment became available, first with liver therapy and later folic acid or vitamin $B_{12}$. The best review of that older literature is by Kinnier Wilson (1940), who described the overlapping syndromes of SCD, peripheral neuropathy, autonomic dysfunction, optic atrophy, mood and behavior changes, psychosis, memory impairment, and cognitive decline.

Although for a period between the late 1940s and the 1960s it was widely assumed, for the reasons described in the historical introduction, that the older literature must have been synonymous with vitamin $B_{12}$ deficiency, this misconception was gradually dispelled from the 1960s onwards as examples of the neurologic complications of megaloblastic anemia due to folic acid deficiency were increasingly recognized. Thus, Grant et al. (1965) described seven cases of spinal cord and peripheral nerve disease; Strachan and Henderson (1967) reported two patients with dementia; and Reynolds et al. (1968) described eight patients with a range of neuropsychiatric associations of anticonvulsant megaloblastic anemia.

In 1972, Pincus et al. described a patient with dementia and SCD. By 1979 Pincus reviewed 25 cases in the literature of SCD associated with folate deficiency. In a general medical hospital population Reynolds et al. (1973) compared the neurologic status of 24 patients with severe folate deficiency and 21 control patients with normal folate levels. A significant increase in organic brain syndrome and pyramidal tract damage was found in the vitamin-deficient group, which was independent of the degree of anemia. In 1976, Manzoor and Runcie reported 10 cases of folate-responsive SCD and neuropathy, some of whom had cognitive and other mental changes. A year later, Botez et al. (1977) summarized 16 cases of a range of peripheral nerve, spinal cord, and mental disorders responsive to folate therapy, most, but not all of whom had megaloblastic anemia. SCD is invariably accompanied by clinical and/or electrical evidence of peripheral neuropathy, but folate deficiency may also cause isolated peripheral neuropathy (Botez et al., 1979a; Shorvon and Reynolds, 1979).

In retrospect it was by now clear that the early 20th century literature must have included patients with megaloblastic anemia due to folate as well as vitamin $B_{12}$ deficiency, as could also be suspected from the number of those earlier patients who had acid in their stomach and were therefore not suffering from "pernicious anemia." It therefore became important to compare the neurologic complications of the two deficiency states which could now be readily separated with vitamin assay techniques. Patients may present to hematologists and physicians with megaloblastic anemia or to neurologists and

*Table 61.1*

**Neuropsychiatric findings in patients with megaloblastic anemia presenting to physicians (Shorvon et al., 1980)**

| | Vitamin $B_{12}$ deficiency (%) | Folic acid deficiency (%) |
|---|---|---|
| Normal | 32 | 35 |
| Organic mental change | 26 | 27 |
| Affective disorder | 20 | 56 |
| Subacute combined degeneration | 16 | 0 |
| Peripheral neuropathy | 40 | 18 |
| Optic atrophy | 2 | 0 |

| Etiology | | | |
|---|---|---|---|
| | Number of cases | | Number of cases |
| Pernicious anemia | 32 | Coeliac disease | 16 |
| Dietary | 8 | Dietary | 8 |
| Gastrointestinal | 7 | Malabsorption | 8 |
| Unexplained | 3 | Unexplained | 2 |
| | n = 50 | | n = 34 |

psychiatrists with predominantly nervous system symptoms. In a prospective study of patients with megaloblastic anemia Shorvon et al. (1980) compared 50 patients with vitamin $B_{12}$ deficiency and 34 with folate deficiency. The neuropsychiatric findings and the causes of anemia are summarized in Table 61.1. The incidence of nervous system involvement was similar, occurring in about two-thirds of each series. About a quarter of each group had cognitive decline. However, peripheral neuropathy was twice as common in vitamin $B_{12}$ deficiency than in folate deficiency. By contrast, depression was more than twice as common in folate deficiency than in vitamin $B_{12}$ deficiency. SCD was uncommon in vitamin $B_{12}$ deficiency but it was not seen at all in 34 patients with folate deficiency, although, as described above, it can be a rare complication of the latter deficiency.

This study confirmed yet again that there is a poor correlation between anemia and nervous system manifestations. As many as a third of each group with a severe deficiency state had no neuropsychiatric complications. There was a considerable overlap between the neuropsychiatric syndromes in the other two-thirds, with a greater emphasis on the spinal cord and peripheral nerves in vitamin $B_{12}$ deficiency and more affective disorder in the folate-deficient group. Some of these differences may perhaps reflect the older age of the vitamin $B_{12}$-deficient patients, two-thirds of whom had pernicious anemia, whereas three-quarters of the folate-deficient group had coeliac disease or other malabsorption syndromes, perhaps resulting in additional deficiency states contributing to the neurologic complications. Nevertheless it is clear that either deficiency state can produce very similar neuropsychiatric syndromes, as is also true of the hematologic manifestations.

## NEUROPSYCHIATRIC DISORDERS WITHOUT ANEMIA OR MACROCYTOSIS

About a quarter of patients with folate-responsive neuropsychiatric disorders do not have anemia or macrocytosis when first seen (Bottiglieri et al., 1995), as is the case for vitamin $B_{12}$ deficiency in about one-fifth of patients (Lindenbaum et al., 1988). There are other neuropsychiatric patients with low serum or red cell folate levels in whom the deficiency may be secondary to the neuropsychiatric disorder for dietary or other reasons but in whom the deficiency may be harmful in the longer term if uncorrected (Reynolds, 1976, 2002b).

Up to one-third of psychiatric, and especially psychogeriatric, hospital admissions have low serum or red cell folate, mostly without anemia or macrocytosis (Reynolds, 1976; Crellin et al., 1993; Bottiglieri et al., 1995). The cause of folate deficiency in these patients has been variously attributed to poor diet, chronic illness, drugs (e.g., barbiturates, alcohol), malabsorption, increased demand, or unknown (Carney and Sheffield, 1970; Bottiglieri et al., 1995). The corresponding

incidence of low serum vitamin $B_{12}$ levels is up to 5% in younger patients but between 10% and 20% in elderly patients (Clarke et al., 2004). Folate deficiency has been consistently associated with evidence of depression (Reynolds et al., 1970; Crellin et al., 1993; Reynolds, 2002a; Ramos et al., 2004; Lewis et al., 2006) and cognitive decline (Sneath et al., 1973; Crellin et al., 1993; Reynolds, 2002a; Ramos et al., 2005), whereas low vitamin $B_{12}$ levels are associated mostly with cognitive impairment (Carney and Sheffield, 1970; Starr et al., 2005).

Neuropsychological studies have suggested general and specific impairments of intellectual function, including attention, episodic and visual spatial memory, and abstract reasoning, which were attributed to folate deficiency (Botez et al., 1979b; Goodwin et al., 1983; Wahlin et al., 2001). In the Kungsholmen (Stockholm) Community Aging and Dementia Project, the pattern of cognitive dysfunction resulting from folate deficiency was said to resemble that in normal aging, i.e., impairment in tasks that involve little structure, are unfamiliar and attention demanding, and involve complex processing of information (Hassing et al., 1999; Wahlin et al., 2001).

There has been continuing debate about the significance of folate deficiency without anemia or macrocytosis in the presence of psychiatric illness, including dementia. For those who have continued to doubt the existence of neuropsychiatric symptoms due to folate deficiency it has been all too easy to assume that the deficiency is secondary to the mental illness for dietary reasons, especially as apathy, withdrawal, and anorexia are common symptoms in depression and dementia. However, nutritional studies have not confirmed this oversimplistic interpretation (Bottiglieri et al., 1995) and it has long been apparent that even when folate deficiency is secondary to mental illness it is an aggravating factor that may lead eventually to a vicious circle of decline (Reynolds, 1976, 2006). Furthermore, impaired motivation and social withdrawal due to deficiency are some of the most folate-responsive symptoms (Reynolds, 1968, 2002b; Manzoor and Runcie, 1976; Botez et al., 1977). In the last two decades evidence of a direct causal link between folate metabolism and some depressions and dementias has been reinforced by studies of homocysteine metabolism.

## FOLATE, HOMOCYSTEINE, DEPRESSION, DEMENTIA, AND AGING

Hyperhomocysteinemia has long been suspected as a possible risk factor for vascular disease (Clarke et al., 2002; McIlroy et al., 2002). However, the lowering of homocysteine concentrations by treatment with folic acid, vitamin $B_{12}$, or vitamin $B_6$ has not been convincingly shown to be effective in the secondary prevention of cardiovascular or cerebrovascular disease, but a possible role for the vitamins in primary prevention is still being evaluated (Kalin and Rimm, 2010). Following the earlier clinical reports, reviewed above, of an association between folate deficiency, depression, and dementia, most, but not all, community-based studies reviewed by Morris (2003) and Morris and Jacques (2010) have suggested that hyperhomocysteinemia and low folate levels are independent risk factors for depression and especially dementia, including both Alzheimer's disease and vascular dementia.

The large prospective Framingham community study indicated that a high plasma homocysteine concentration doubled the risk of developing either Alzheimer's disease or other dementias (Seshadri et al., 2002). Similarly, a Swedish community study suggested that low levels of serum folate or vitamin $B_{12}$ doubled the risk of Alzheimer's disease (Wang et al., 2001). In a retrospective study of the survivors of the Scottish Mental Surveys of 1932 which included childhood IQ, plasma homocysteine concentration accounted for 7–8% of the variance in cognitive performance (Duthie et al., 2002). A prospective Italian population-based study confirmed that high plasma homocysteine and low serum folate values were independent predictors of dementia and Alzheimer's disease, whereas the association with vitamin $B_{12}$ was not significant (Ravaglia et al., 2005). In the American Veteran Affairs Normative Aging Study high homocysteine and low folate levels predicted cognitive decline in aging men (Tucker et al., 2005). In a community study of 518 elderly patients without dementia in South Korea 45 (8.7%) developed dementia, three-quarters with Alzheimer's disease, over a prospective follow-up period of 2.4 years. Incident dementia was predicted by baseline low folate, but not by vitamin $B_{12}$ or homocysteine levels. However, the onset of dementia was also more strongly associated with an exaggerated decline in folate and rise in homocysteine, although weakened by adjustment for weight loss (Kim et al., 2008). According to Morris and Jacques (2010), the few inconsistent epidemiologic studies appear explicable by selection factors, misclassification and confounding.

There is substantial overlap between Alzheimer's disease and vascular dementia, and the separation of these two diseases from each other and from other dementias is not easy in life even with the most sophisticated techniques (Neuropathology Group of the Medical Research Council's Cognitive Function and Ageing Study, 2001). Therefore neuropathologic studies are of particular importance. In a case controlled study of 164 patients with Alzheimer's disease, 76 of whom were confirmed neuropathologically, Alzheimer's disease

was significantly associated with high plasma homocysteine and low serum folate and vitamin $B_{12}$ (Clarke et al., 1998). Higher plasma homocysteine was associated with a more rapid atrophy of the medial temporal lobes over 3 years. In 12 patients high homocysteine was also significantly associated with confirmed vascular dementia. In people without dementia plasma homocysteine was inversely related to magnetic resonance imaging (MRI) measures of hippocampal and cortical volume (den Heijer et al., 2003). However, poor cognitive ability associated with high homocysteine concentrations was independent of structural brain changes on MRI (Prins et al., 2002). In a prospective study of 30 nuns from the same environmental and nutritional background who died at age 78–101 years, half had neuropathologic confirmation of Alzheimer's disease. Of 18 nutritional factors examined only serum folate was correlated with atrophy of the neocortex, especially in the 15 nuns with Alzheimer's disease but also in those with minimal atherosclerosis and no infarcts (Snowdon et al., 2000).

One reason for the apparently high incidence of folate deficiency and hyperhomocysteinemia in elderly people is that folate levels in serum and CSF fall and plasma homocysteine rises with age (Bottiglieri et al., 2000a; Seshadri et al., 2002; Serot et al., 2005), perhaps contributing to the aging process (Wahlin et al., 2001; Reynolds, 2002a, 2006). Interestingly the pattern of cognitive dysfunction associated with folate deficiency was noted to be similar to that in normal aging (Hassing et al., 1999; Wahlin et al., 2001), while the domains of cognitive function which improved in normal subjects with folate supplementation for 3 years were those that tend to decline with age (Durga et al., 2007a).

Raised plasma homocysteine levels have been observed in up to 30% of patients with severe depression (Fava et al., 1997; Bottiglieri et al., 2000b; Morris and Jacques, 2010). Bottiglieri et al. (2000b) have described a biological subgroup of depressed patients with high plasma homocysteine concentrations, folate deficiency, and impaired monoamine neurotransmitter metabolism. In an Australian study low folate and high homocysteine, but not vitamin $B_{12}$, were correlated with depressive symptoms in community-dwelling middle-aged individuals. The effects of folate and homocysteine were overlapping but distinct (Sachdev et al., 2005). In a large Norwegian community study hyperhomocysteinemia and the folate polymorphism MTHFR 677C→T were associated with depression, but not anxiety, in middle-aged, but not elderly, patients (Bjelland et al., 2003). The relationship of MTHFR 677C→T polymorphisms and depression was supported by Lewis et al. (2006), but this has also been noted with cognitive impairment (Durga et al., 2006).

## FOLIC ACID AND EPILEPSY

Folate deficiency induced by some of the older antiepileptic drugs, e.g., phenytoin or barbiturates, was commonly associated with mental changes, especially depression, apathy, psychomotor retardation, and cognitive decline (Reynolds, 1968, 1976). Although folate deficiency in epileptic patients appears less common since the newer antiepileptic drugs, e.g., carbamazepine and valproate, have become available, more recent studies have revealed hyperhomocysteinemia in up to 40% of adults and 15% of children with epilepsy (Schwaninger et al., 1999; Huemer et al., 2005). High homocysteine levels are significantly related to antiepileptic medication and to low folate levels and are normalized by treatment with folic acid, 1 mg daily for 3 months (Huemer et al., 2005). Antiepileptic medication is associated with an increased risk of major congenital malformations, including neural tube defects (NTD), but it is unclear to what extent these birth defects are mediated by folate mechanisms or prevented by prophylactic periconceptual folic acid (Morrow et al., 2009) (see section below on neural tube defects).

Treatment of 26 patients with epilepsy and drug-induced folate deficiency with 15 mg of folic acid daily *for 1–3 years* resulted in improved drive, initiative, alertness, concentration, mood and sociability in most and an increase in seizure frequency in some (Reynolds, 1968). Controlled trials of folate therapy for *up to 3 months* produced inconsistent results, but there is abundant experimental evidence that folate derivatives have excitatory properties, especially when the efficient blood–brain barrier mechanism for the vitamin is circumvented (Reynolds et al., 1972; Reynolds, 1976; Hommes et al., 1979). In laboratory animals intravenous sodium folate will only induce seizures in very large doses; but if the blood–brain barrier is damaged locally by trauma or a heat lesion the dose required for an epileptogenic effect is much lower; and if the blood–brain barrier is circumvented by intraventricular or intracortical administration all folate derivatives are highly convulsant (Hommes et al., 1973, 1979). Furthermore the vitamin enhances the kindling model of epilepsy and can even be used to kindle seizures directly (Miller et al., 1979). It is uncertain how folates induce their excitatory effects but they may do so by blocking or reversing GABA-mediated inhibition (Davis and Watkins, 1973). Excitatory phenomena produced by folates resemble those induced by disinhibitory compounds such as bicuculline, penicillin, or picrotoxin (Hommes et al., 1979).

The risk of aggravating seizures in patients with epilepsy is small because the blood–brain barrier limits entry of folic acid, but the risk increases with larger doses over longer times (Reynolds, 1976,

2002b). The vitamin can also lower blood phenytoin levels which may be an additional possible aggravating mechanism (Rivey et al., 1984).

## TREATMENT ISSUES

Reports from the 1960s and 1970s of folate-responsive neurologic disorders, usually but not always associated with megaloblastic anemia, have been described above. Considering that a third of patients with folate (or vitamin $B_{12}$) deficiency severe enough to produce anemia have no immediate nervous system involvement (Shorvon et al., 1980), the significance of folate deficiency in the presence of neuropsychiatric disorders without anemia or macrocytosis is not always clear, especially in the elderly (Bottiglieri et al., 1995; Reynolds, 2002a). However, if this deficiency, whether primary or secondary, is not already affecting the nervous system, it is highly likely to do so in the longer term if left untreated (Reynolds, 2002b, 2006).

The neurologic response to folate treatment is usually slow over many weeks and months, at least in part because of the efficient blood–brain barrier mechanism for this vitamin which limits entry, perhaps because of its excitatory properties (Hommes et al., 1973; Reynolds, 1976, 2002b). Treatment is recommended for at least 6 months, but some improvement should be detected within 2–3 months. The response and the degree of residual disability will be related to the duration and severity of nervous system manifestations before treatment.

### Depression

In patients with depression the presence of folate deficiency is associated with a poorer response to standard antidepressant therapy (Reynolds et al., 1970; Papakostas et al., 2005). Six controlled trials for periods varying from 8 weeks to 1 year have confirmed an effect of folates on mood and social recovery either directly or mostly in addition to psychotropic treatment in psychiatric patients mainly with depression (Botez et al., 1979b; Coppen et al., 1986; Godfrey et al., 1990; Passeri et al., 1993; Coppen and Bailey, 2000; Papakostas et al., 2012). The details of the trials and outcomes are summarized in Table 61.2. The trials have utilized folic acid or more recently methylfolate, both with positive outcomes. Which formulation is best is uncertain but methylfolate is the transport form across the blood–brain barrier and has theoretical advantages.

Recently, Papakostas et al. (2012) reported that 7.5 mg of L-methylfolate for 30 days was ineffective but 15 mg for 60 days significantly improved mood

*Table 61.2*

**Controlled clinical trials of folate in depressive disorders**

| Authors | Patients | Number | Trial design | Outcome |
|---|---|---|---|---|
| Botez et al., 1979 | Depression<br>Folate deficiency | 24 | Folic acid 15 mg daily versus placebo; 4 months | Improved mood, Wechsler IQ memory scale and Kohs block design |
| Coppen et al., 1986 | Manic depression<br>On lithium | 102 | Folic acid 200 μg daily versus placebo; 1 year | Lower affective morbidity index associated with higher end of trial serum folate levels |
| Godfrey et al., 1990 | Major depression<br>Schizophrenia<br>Red cell folate < 200 μg/L<br>On standard psychotropic medication | 41 | Methylfolate 15 mg daily versus placebo; 6 months | Enhanced clinical social recovery in depression and schizophrenia increasing over time |
| Passseri et al., 1993 | Elderly depression with moderate dementia | 96 | Methylfolate 50 mg daily versus trazodone 100 mg daily; 8 weeks | Similar outcome in mood (Hamilton scale) in both groups |
| Coppen and Bailey 2000 | Depression on fluoxetine | 127 | Folic acid 500 μg daily versus placebo; 10 weeks | Enhanced mood outcome, especially in women |
| Papakostas et al., 2012 | Major depression<br>SSRI-resistant | 148 | L-methylfolate 7.5 mg daily versus placebo; 30 days | No significant differences |
| | | 75 | L-methylfolate 15 mg daily versus placebo; 60 days | Improved response rate and reduction in depression scores |

and outcome in patients with major depression who were SSRI-resistant. Earlier Godfrey et al. (1990) had reported increasing clinical and social recovery over 6 months in major depressive and schizophrenic patients with definite or borderline folate deficiency, in whom 15 mg of methylfolate was added to standard psychotropic medication. The folate status of the patients in the trial by Papakostas et al. (2012) was not reported, but there is preliminary evidence of an antidepressant effect of methylfolate monotherapy in the absence of folate deficiency (Passeri et al., 1993; Bottiglieri et al., 1995), but with a greater rise in red cell folate in responders than nonresponders (Bottiglieri et al., 1995; Reynolds, 2006). An important clue is the mood-elevating properties of nitrous oxide, i.e., laughing gas. This euphoriant effect of nitrous oxide is very probably related to the instantaneous inactivation of methionine synthase leading to an acute rise in methylfolate in the brain (Reynolds, 2006). (See section on metabolic mechanisms, below).

### Cognitive function

A few controlled trials, reviewed recently by Morris and Jacques (2010), of the effect of the vitamin on cognitive function in elderly patients, with or without impaired cognitive function, have been more inconsistent. The latter authors confirm the importance of separating studies of patients who are folate-deficient from those in whom the vitamin was given (usually together with vitamin $B_{12}$ and vitamin $B_6$) to lower homocysteine levels, the latter mostly in the absence of cognitive impairment but with a view to preventing future deterioration. For example, in folate-deficient subjects with mild to moderate cognitive impairment Fioravanti et al. (1997) reported that folic acid 15 mg daily for 60 days significantly improved attention and memory recall in comparison to placebo. In the largest and longest study to date, Durga et al. (2007a), who also reviewed earlier trials, reported that in normal subjects aged 50–70 years with raised plasma homocysteine levels, supplementation with 800 μg folic acid daily for 3 years significantly improved memory, information processing speed and sensorimotor speed compared with placebo. They also noted that the improvements were in domains of cognitive function that tend to decline with age. Although 98% of subjects had normal folate levels at basline the cognitive benefits were generally 2–5 times greater in those with relatively lower red cell folate concentrations (Durga et al., 2007b).

Some of the inconsistencies in clinical trials are partly related to unsolved questions about dose and duration of therapy, whichever formulation is utilized. In experimental studies of repair in the adult nervous system Iskandar et al. (2010) reported that regeneration of afferent spinal neurons was biphasic and dose-dependent, and correlated closely over its dose range with global and gene-specific DNA methylation. It is also relevant that the adverse neurologic effects of folic acid in the presence of vitamin $B_{12}$ deficiency are related both to the dose and the duration of folate therapy (Schwartz et al., 1950; Savage and Lindenbaum, 1995). In clinical studies small doses of the vitamin over the longer term may be preferable to larger doses in the short or long term, not least because of the risks to the nervous system, especially in vitamin $B_{12}$ deficiency and epilepsy (Reynolds, 2002b). A positive response is more likely in the presence of confirmed folate deficiency.

Studies of homocysteine lowering treatment with combined vitamin $B_{12}$, vitamin $B_6$, and folic acid are beyond the scope of this review, but it is of interest that treatment with this combination of vitamins for 2 years in the VITACOG trial has been reported to slow the rate of cognitive decline and brain atrophy in elderly subjects with mild cognitive impairment (de Jager et al., 2012).

## NEURAL TUBE DEFECTS AND THEIR PREVENTION

Birth defects probably arise from a complex interplay of genetic, epigenetic, environmental, and lifestyle factors. The prevalence of neural tube defects (NTD) varies from 0.8 per 1000 births in areas of the US to 13.8 per 1000 in areas of China. Worldwide approximately 300 000 children are born each year with NTD (Hobbs et al., 2010).

Since the early reports of Hibbard (1964) and Smithells et al. (1981), abundant evidence has confirmed that impaired maternal folate intake and status, including the administration of folate antagonists, significantly increases the risk of NTD (MRC Vitamin Study Group, 1991; Hernandez-Diaz et al., 2000; Massaro and Rogers, 2002; Hobbs et al., 2010). This evidence has led to numerous case control and cohort studies as well as two nonrandomized and four randomized trials showing that periconceptual preventive administration of varying doses of folic acid significantly reduced the risk of NTD, but approximately one-third of NTD are not preventable by folic acid (MRC Vitamin Study Group, 1991; Hobbs et al., 2010). For the last two decades many countries have had a public policy of recommending 400 μg of folic acid prior to any pregnancy, especially in those deemed to be at special risk for genetic or nutritional reasons.

As many women either do not receive or do not accept this prophylactic advice several countries have, in the last 15 years, introduced mandatory fortification of grain, flour, or cereals. In the US, Canada, Chile, Costa Rica, and South Africa, many community studies, reviewed

by Berry et al. (2010), have reported a reduction of the prevalence of NTD of between approximately 20% and 50%, on average about one-third. However, fortification has sometimes resulted in higher intake of folic acid than predicted (Choumenkovitch et al., 2002) and some countries, notably the UK and New Zealand, have refrained from fortification because of concerns about masking or aggravating vitamin $B_{12}$ deficiency in the elderly and uncertainty over cancer risks. A report from Chile questions a possible increase in the incidence of SCD (Nogales-Gaete et al., 2004).

The mechanisms by which impaired maternal folate status increase risk and prophylactic folic acid reduces risk, even in mothers with apparently normal folate status, are largely unknown (Massaro and Rogers, 2002; Wallis et al., 2010). The focus is again on genetic and epigenetic mechanisms involving nucleotide synthesis and/or DNA methylation. There is much interest in various genetic polymorphisms of folate enzymes, especially the MTHFR 677C→T variant, but also others (Blom et al., 2006; Van der Linden et al., 2006), the presence of which in the population increases the risk of NTD (Christensen and Rozen, 2010). Vitamin $B_{12}$ and homocysteine have also been implicated (Ray and Blom, 2003; Wallis et al., 2010). Autoantibodies to the folate receptor-α have been detected in up to three-quarters of mothers who had given birth to a child with a NTD (Rothenberg et al., 2004). It is clear that folate is critical to normal fetal development and the search is ongoing for the factors that might impair uptake or metabolism of folate by fetal cells (Wallis et al., 2010).

## DISORDERS OF FOLATE METABOLISM IN INFANCY AND CHILDHOOD

An increasing number of rare inherited or acquired disorders of the absorption, transport, or metabolism of folate and vitamin $B_{12}$ have been recognized over several decades. This is a highly specialized subject requiring sophisticated metabolic and genetic services attached to centers of pediatric neurology or child health and is beyond the scope of this chapter. Good reviews are those of Rosenblatt and Fenton (2001), Surtees (2001), and Whitehead (2006).

The commonest inborn error of folate metabolism is methylenetetrahydrofolate reductase (MTHFR) deficiency due to several mutations of varying severity of the *MTHFR* gene. Others include hereditary folate malabsorption and glutamate formiminotransferase-cyclodeaminase deficiency, both autosomal recessive disorders. The most recent disorder is cerebral folate deficiency (Ramaekers and Blau, 2004), associated with normal blood levels of folate and homocysteine, due to a defect in the transport activity of folate receptor-α (FRα), in turn associated with circulating antibodies to the receptor (Rothenberg et al., 2004). Mutations in the *FOLR1* gene that expresses FRα have been identified in a few families (Cario et al., 2009; Steinfeld et al., 2009).

*Table 61.3*

**Clinical neurologic features in remethylation defects related to age of presentation (Ogier de Baulny et al., 1998)**

| |
|---|
| **1. Neonatal and early infancy (<3 months):** |
| Poor feeding |
| Lethargy |
| Hypotonia/hypertonia |
| Seizures |
| Coma |
| **2. Late infancy and early childhood (>3 months to < 10 years):** |
| Slow development |
| Lethargy |
| Mental deterioration |
| Encephalopathy |
| Seizures |
| Spastic paresis (subacute combined degeneration) |
| Extrapyramidal signs |
| Neuropathy |
| **3. Late childhood and early adulthood (>10 years):** |
| Previous mild retardation |
| Mental deterioration |
| Behavior disturbance |
| Encephalopathy |
| Myelopathy (subacute combined degeneration) |
| Neuropathy |

This subject is impossible to separate from that of inborn errors or vitamin $B_{12}$ metabolism, of which there are even more examples. Such is the clinical and metabolic overlap that some authors integrate most of the inborn errors of either vitamin under the heading of "defects in remethylation" (Ogier de Baulny et al., 1998). The similar clinical features of these genetically dissimilar disorders of either folate or vitamin $B_{12}$ metabolism are best categorized according to the age of presentation and are well summarized in Table 61.3 (Ogier de Baulny et al., 1998).

## CLINICAL DISSOCIATION

For over a century it has been well documented that there is a poor correlation between the hematologic and neuropsychiatric manifestations of folic acid and vitamin $B_{12}$ deficiency, i.e., both before and after the two vitamin deficiencies were separated in the late 1940s (Kinnier Wilson, 1940; Schwartz et al., 1950; Chanarin, 1969; Reynolds, 1976; Shorvon et al.; 1980; Lindenbaum et al., 1988). There is no doubt that some patients may present to hematologists without any evidence of neuropsychiatric disorder (e.g., Shorvon et al., 1980) but that

other patients present to neurologists or psychiatrists with no anemia or even macrocytosis (e.g., Lindenbaum et al., 1988). Many other patients present with varying degrees of involvement of both blood and nervous systems. This clinical dissociation has led to repeated suggestions that the nervous system complications must have a different mechanism to the megaloblastic anemia (Chanarin, 1969; Lindenbaum et al.; 1988; Healton et al., 1991). To some extent the dissociation is illusory and is influenced by the timing of the diagnosis, especially the relatively early modern diagnosis of hematologic involvement by screening techniques. In the first third of the 20th century, before any treatment was available, patients would eventually progress at different rates to nearly 100% association between anemia and neuropsychiatric disorder (Woltmann, 1919; Ahrens, 1932; Kinnier Wilson, 1940). Furthermore this clinical dissociation between two separate complications of a single metabolic disorder is not unique to folic acid or vitamin $B_{12}$ deficiency, but seems common to all general metabolic disorders that also affect the nervous system (Reynolds, 1976). For example, Wilson's disease may present either to a neurologist or hepatologist with predominantly cerebral or hepatic involvement; likewise, hypothyroidism may present either to an endocrinologist, a neurologist or a psychiatrist. There are several possible reasons for these divergences including the highly specialized structure, environment and function of the nervous system in comparison to other organs, especially the blood, but they need not and usually do not imply any fundamental difference in the metabolic basis of the neural manifestations (Reynolds, 1976, 2006).

Misunderstandings arose in the late 1940s and early 1950s when it was noted that the administration of large doses of folic acid to patients with undoubted vitamin $B_{12}$ deficiency was often associated with suboptimal improvement in the anemia, apparently associated with precipitation or aggravation of neurologic complications. This gave rise to the theory that the improvement in the anemia by the administration of folic acid masked and delayed the diagnosis of vitamin $B_{12}$ deficiency, allowing the neurologic disorder to progress (Chanarin, 1969). However, this misinterpretation did not accurately reflect what was actually reported in the middle of the 20th century. Careful review of that literature shows that after giving folic acid to treat "pernicious anemia" there was sometimes brief temporary symptomatic neurologic improvement before the more florid and sometimes explosive deterioration (Hall and Watkins, 1947; Schwartz et al., 1950). Furthermore after the obvious but suboptimal hematologic improvement there was commonly a later insidious hematologic relapse (Hall and Watkins, 1947; Schwartz et al., 1950). Eventually similar numbers of patients have neurologic and hematologic relapse, although often again dissociated (Schwartz et al., 1950). In other words, both the nervous system and the blood may show improvement and relapse but to different degrees and at different rates, which may in turn reflect profound differences in structure, function, and cellular turnover in the two tissues. Occasional reports of neurologic deterioration due to untreated vitamin $B_{12}$ deficiency during folate treatment continue to occur (Dhar et al., 2003).

There is some evidence that in patients with vitamin $B_{12}$ deficiency there is an inverse correlation between the degree of anemia and the degree of neurologic disability (Healton et al., 1991). Furthermore, patients with neurologic complications of vitamin $B_{12}$ deficiency have significantly higher serum folate concentrations than those without nervous system disorders (Waters and Mollin, 1961; Reynolds, 1979b). In a large scale community-based study of elderly subjects in the US, Morris et al. (2007) reported a greater cognitive decline in patients with high serum folate levels associated with low serum vitamin $B_{12}$ levels compared with those with more modest folate levels in association with vitamin $B_{12}$ deficiency. This was not confirmed in a subsequent UK study where there is no folate fortification policy (Clarke et al., 2008). However, in a more recent prefortification prospective epidemiologic study in Framingham in the US, low or "low normal" plasma vitamin $B_{12}$ levels in conjunction with high plasma folate or supplemental folate predicted especially rapid cognitive decline (Morris et al., 2012). The American studies were supported by evidence of increasing homocysteine and methylmalonic acid levels in patients with vitamin $B_{12}$ deficiency and increasing folate levels (Selhub et al., 2007). All studies confirm an intimate relationship between folate and vitamin $B_{12}$ in both blood and nervous system, but at the moment there is little reason to doubt that the nature of this relationship is fundamentally any different in blood and nervous system.

## METABOLIC MECHANISMS

The key to the metabolic understanding of both the neurology and hematology of both folate and vitamin $B_{12}$ deficiency is the synthesis of methionine from homocysteine by methionine synthase in which both 5-methyltetrahydrofolate and methyl vitamin $B_{12}$ act as cofactors (Fig. 61.1). Failures in the availability, absorption and delivery of folate through the folate cycle and therefore the supply of methyl groups, or in the availability of vitamin $B_{12}$, would have similar and overlapping consequences on both blood and nervous system.

The megaloblastic anemia in either deficiency state is due to impairment of DNA synthesis, integrity and transcription, associated with failures in the synthesis of

purines and especially thymidine (Chanarin, 1969; Stabler, 2010). In folate deficiency there is a failure of delivery of methyl folate; in vitamin $B_{12}$ deficiency, especially pernicious anemia, there is a block in the utilization of methyl folate, commonly leading to a rise in plasma folate, the so-called methyl-folate trap. Either mechanism leads to a morphologically indistinguishable megaloblastic anemia.

There is evidence that similar mechanisms apply to the neurologic disorders in these two deficiency states (Reynolds, 1976, 2006). However, the nervous system is also much more complex and hierarchical than the hemopoietic system and includes metabolic pathways that have little or no role in the blood, e.g., in relation to myelin or mood. Nor should we assume that all neuropsychiatric complications have exactly the same metabolic basis, as the failure of methylation can involve numerous metabolic pathways that require a supply of methyl groups through the methyl donor *S*-adenosyl methionine, including the methylation of DNA which plays a vital part in gene expression and other epigenetic mechanisms (Rampersaud et al., 2000; Friso and Choi, 2002; Bottiglieri and Reynolds, 2010).

An important model is that of nitrous oxide, which in man can produce megaloblastic changes in bone marrow within hours of anesthesia and the full range of neuropsychiatric complications within weeks or months of abuse (Layzer, 1978; Nunn, 1987), and which has been studied in several species including monkeys, pigs, rats, and fruit bats (Scott et al., 1994). By oxidizing the cobalt atom of vitamin $B_{12}$, nitrous oxide mimics vitamin $B_{12}$ deficiency, rapidly inactivating methionine synthase (Fig. 61.1). Methionine protects against nitrous oxide-induced subacute combined degeneration implying that methylation processes are important in this disorder (Scott et al., 1994). The methylation hypothesis is also supported by results of studies of demyelination in inborn disorders of remethylation (Surtees, 1998). I have suggested that the euphoriant laughing gas effect of nitrous oxide in man is due to the rapid raising of methyl folate concentrations in the nervous system, consequent upon the almost instantaneous inactivation of vitamin $B_{12}$ (Reynolds et al., 1984; Reynolds, 2006).

Table 61.4 summarizes postulated mechanisms not only for the neuropsychiatric complications of folate and vitamin $B_{12}$ deficiency but also for the possible protective effect of folate in some disorders not primarily due to deficiency. As already discussed, folic acid can reduce the incidence of neural tube defects in the early embryonic period even in the absence of folate deficiency (Massaro and Rogers, 2002; Hobbs et al., 2010). Iskandar et al. (2004, 2010) reported that folic acid significantly improved the regrowth of sensory axons in a spinal cord regeneration model and improved neurologic recovery from spinal cord contusion injury in rats. Furthermore such repair occurs at least in part through DNA methylation, implicating an epigenetic mechanism in CNS recovery (Kronenberg and Endres, 2010). Folates seem to be of fundamental importance in brain growth, differentiation, development, repair, mood, cognition

*Table 61.4*

**Proposed metabolic mechanisms of folate/vitamin $B_{12}$ neurologic disorders**

| | Clinical implications of folate/vitamin $B_{12}$ deficiency or inborn errors | Postulated metabolic mechanisms |
|---|---|---|
| Embryo<br>Fetus<br>Infant<br>Child | Disorders of CNS growth and fetal development | Impaired DNA synthesis, transcription; impaired genomic methylation and epigenetic mechanisms |
| Adult | SCD/neuropathy | As above and impaired nongenomic methylation, e.g., myelin proteins, phospholipids |
| | Depression/psychiatric disorders | Impaired genomic and nongenomic methylation, e.g., monoamines, biopterins. Impaired excitation |
| Elderly | Brain aging<br>Cognitive decline | All the above mechanisms including DNA synthesis, genomic and nongenomic methylation, e.g., proteins, phospholipids, choline |
| | Dementia | Failure of repair mechanisms |
| Other | Alzheimer's disease | All the above mechanisms, oxidative stress, and increased β-amyloid formation |
| | Cerebrovascular disease and stroke | Homocysteine-related vascular mechanisms |

CNS, central nervous system; SCD, subacute combined degeneration of the cord.

and aging (Reynolds, 2002a, 2006; Massaro and Rogers, 2002; Mattson and Shea, 2003; Lucock, 2004; Bottiglieri and Reynolds, 2010). Many of these functions and their breakdown in folate and vitamin $B_{12}$ deficiency are probably primarily mediated through nucleotide synthesis, DNA integrity and transcription, and epigenetic mechanisms including gene expression, involving DNA methylation. As in megaloblastosis these mechanisms are probably involved in most, if not all the neurologic complications of deficiencies or inborn errors of folic acid or vitamin $B_{12}$, a kind of "megaloblastosis" of the nervous system (Reynolds, 2006). However, in addition there is widespread failure of nongenomic methylation involving potentially numerous S-adenosyl methionine-mediated methylation reactions in many neural pathways (Bottiglieri et al., 1990, 1994; Bottiglieri and Reynolds, 2010). Possible examples are myelin basic protein and membrane phospholipids, which may perhaps contribute to demyelination (Surtees et al., 1991; Scott et al., 1994; Bottiglieri and Reynolds, 2010). Methylation and turnover of monoamines and biopterins have been implicated in depression and perhaps other psychiatric symptoms in the context of folate deficiency (Reynolds et al., 1970; Bottiglieri et al., 1992; Bottiglieri and Reynolds, 2010). There is clinical evidence that the turnover of monoamines is increased by both folic acid and *S*-adenosylmethionine (Bottiglieri et al., 1990, 2000b; Bottiglieri and Reynolds, 2010).

There is also widespread interest in the role of homocysteine in vascular disease and dementia including Alzheimer's disease (Morris, 2003; Irizarry et al., 2005; Ravaglia et al., 2005; Bottiglieri and Reynolds, 2010). It is therefore of interest in relation to aging, cognitive decline, and various forms of dementia that serum and CSF folate concentrations fall and serum homocysteine concentrations rise with age (Reynolds, 2006; Bottiglieri and Reynolds, 2010). It has also been suggested that homocysteine-related impairment of glutathione metabolism and oxidative stress (McCaddon et al., 2003) or impaired DNA methylation and associated epigenetic mechanisms may increase amyloid-β-peptide production and toxicity in Alzheimer's disease (Kruman et al., 2002; Fuso et al., 2005, 2008; Irizarry et al., 2005; Bottiglieri and Reynolds, 2010).

Vulnerability to all the above mechanisms will be increased in relation to both the severity and duration of either folic acid or vitamin $B_{12}$ deficiency (Reynolds, 1976, 2002a; Shorvon et al., 1980; Bottiglieri et al., 1995), in the presence of predisposing genetic factors, including polymorphisms of folate and vitamin $B_{12}$-dependent enzymes, especially if the latter are additionally compromised by dietary factors, i.e., nutrigenomics (Friso and Choi, 2002; Lucock, 2004; Durga et al., 2006; Bottiglieri and Reynolds, 2010), or in the presence of associated metabolic disorders, such as malabsorption, or pharmacologic stress, e.g., folate antagonists (Shorvon et al., 1980; Reynolds, 2006).

## CONCLUSIONS

In the last 50 years there has been a remarkable transformation in our understanding of the role of folates in nervous system disorders. The misconceptions of the late 1940s and 1950s that there was no neurology of folic acid deficiency and that folic acid administration was only harmful to the nervous system, have gradually been replaced by a recognition that the neuropsychiatric manifestations of folic acid deficiency, with or without megaloblastic anemia or macrocytosis, overlap considerably with those associated with vitamin $B_{12}$ deficiency, as is also the case for the megaloblastic anemias of either vitamin deficiency.

In the early stages there is often dissociation between the neuropsychiatric and hematologic expression of the vitamin deficiency, as occurs in other general metabolic disorders that affect the nervous system. The occurrence of nervous system complications is influenced by the duration as well as the severity of the deficiency, by predisposing genetic factors, including polymorphisms of folate-dependent enzymes, and by any associated metabolic disorders. The administration of folic acid in the presence of vitamin $B_{12}$ deficiency may be harmful to the nervous system and ultimately to the blood. The vitamin should be used with caution in epilepsy. Overall the benefits greatly exceed the risks but the latter should not be dismissed as of no importance. Both benefits and risks are influenced by the dose and duration of treatment.

In the nervous system, as in the blood, failure or blocking of the supply of methyl groups will result in impaired purine, thymidine, nucleotide and DNA synthesis and in disruption of DNA transcription, gene expression, and other epigenetic mechanisms affecting fetal and tissue growth, differentiation, and repair. In addition, impaired methylation of proteins, lipids, and monoamines may contribute to the varied neuropsychiatric disorders, including depression and cognitive decline. There is now great interest in the role of folate and its related metabolic pathways in nervous system function and disease at all ages and the potential use of the vitamin in the prophylaxis of some disorders of nervous system development, mood, and cognition, including the aging process.

## SUMMARY

The metabolism of folic acid and the metabolism of vitamin $B_{12}$ are intimately linked such that deficiency of either vitamin leads to an identical megaloblastic

anemia. The neurologic manifestations of folate deficiency overlap with those of vitamin $B_{12}$ deficiency and include cognitive impairment, dementia, depression and, less commonly, peripheral neuropathy and subacute combined degeneration of the spinal cord. In both deficiency states there is often dissociation between the neuropsychiatric and the hematologic complications. There is a similar overlap and dissociation between neurologic and hematologic manifestations of inborn errors of folate and vitamin $B_{12}$ metabolism.

Low folate and raised homocysteine levels are risk factors for dementia, including Alzheimer's disease, and depression. Even when folate deficiency is secondary to psychiatric illness due to apathy or poor diet it may eventually aggravate the underlying disorder in a vicious circle effect. Clinical responses to treatment with folates are usually slow, over weeks and months, probably due to the efficient blood–brain barrier mechanism for the vitamin, perhaps in turn related to the experimentally demonstrated excitatory properties of folate derivatives. The inappropriate administration of folic acid in the presence of vitamin $B_{12}$ deficiency may lead to both neurologic and, later, hematologic relapse.

Impaired maternal folate intake and status increases the risk of neural tube defects. Periconceptual prophylactic administration of the vitamin reduces, but does not eliminate the risk of neural tube defects even in the absence of folate deficiency. Folates and vitamin $B_{12}$ have fundamental roles in central nervous system function at all ages, especially in purine, thymidine, neucleotide, and DNA synthesis, genomic and nongenomic methylation and, therefore, in tissue growth, differentiation, and repair. There is interest in the potential role of both vitamins in the prevention of disorders of central nervous system development, mood, dementia, including Alzheimer's disease, and aging.

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