# Folic acid, ageing, depression, and dementia

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It is becoming clear that folic acid affects mood and cognitive function, especially in older people. Edward Reynolds draws together the evidence

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Folic acid is important for functioning of the nervous system at all ages.[1–4] In the fetus the relation between maternal folate status and the risk of neural tube defects is well established: clinical trials have shown that periconceptual preventive treatment with 400 µg or higher of folic acid significantly reduces the risks of such defects.[4]

In neonates, infants, children, and adolescents, inborn errors of folate transport and metabolism are associated with a variety of overlapping syndromes which are influenced by age of clinical presentation. These include developmental delay, cognitive deterioration, motor and gait abnormalities, behavioural or psychiatric symptoms, seizures, signs of demyelination or failure of myelination, and vascular changes seen on magnetic resonance imaging or postmortem examination.[4] Less commonly, subacute combined degeneration and peripheral neuropathy may also occur.

In adult patients presenting with megaloblastic anaemia due to folate deficiency, approximately two thirds have neuropsychiatric disorders which overlap considerably with those associated with anaemia due to vitamin B-12 deficiency.[2 5] However, depression is commoner in patients with folate deficiency, and subacute combined degeneration with peripheral neuropathy is more frequent in those with vitamin B-12 deficiency. The degree of anaemia is poorly correlated with the presence of neuropsychiatric disorders, but if these anaemias were left untreated nearly all patients would eventually develop neuropsychiatric complications.[2] Over the past 35 years numerous studies have shown a high incidence of folate deficiency correlated with mental symptoms, especially depression and cognitive decline in epileptic, neurological, psychiatric, geriatric, and psychogeriatric populations.[3 4] Furthermore, recent studies in elderly people suggest a link between folic acid, homocysteine, ageing, depression, and dementia, including Alzheimer's disease and vascular disease.[4 6–9]

In this paper I review the evidence relating folate deficiency to depression and dementia, especially in the ageing nervous system.

## Summary points

- Folate deficiency is associated with depression and dementia
- In elderly people it may be related to ageing, poor diet, malabsorption, drugs, or increased demand or be unexplained
- Folic acid has particular effects on mood and cognitive and social function
- Impaired folate metabolism may result in a pattern of cognitive dysfunction that resembles ageing
- The duration of folate deficiency and of its treatment is as important as the degree of deficiency and the dose of folic acid
- Folic acid should be used with caution in the presence of vitamin B-12 deficiency or epilepsy
- Folic acid is important in the nervous system at all ages, but in elderly people deficiency contributes to ageing brain processes, increases the risk of Alzheimer's disease and vascular dementia and, if critically severe, can lead to a reversible dementia

## Patients with epilepsy

Many studies of folate in serum, red cells, or cerebrospinal fluid have shown a consistent association between drug induced deficiency and mental changes, especially depression, apathy, psychomotor retardation and dementia.[3 4]

Treatment of 26 folate deficient epileptic patients with 5 mg of folic acid daily for one to three years resulted in improved drive, initiative, alertness, concentration, mood, and sociability in most.[1] This contradicted the prevailing view that folic acid was harmful only to the nervous system, although that concept was reinforced by the additional observation that seizure control deteriorated in several of the patients. Although short term clinical trials of folic acid for one to three months produced conflicting results with respect to mental changes and seizure control, there is abundant experimental evidence now of the excitatory properties of folate derivatives, especially when the efficient blood-brain barrier mechanism for the vitamin is circumvented.[4 10] In addition, folic acid influences phenytoin metabolism, leading to a fall in blood concentrations of this drug.

## Neurological patients

Several of the earliest reports of neurological disease associated with severe folate deficiency emphasise the importance of dementia and depression reversible with vitamin therapy.[2 11–13] For example, Botez et al described 16 patients whose impaired intellectual function, confirmed on neuropsychological testing, was strikingly improved after six to 12 months of folic acid therapy. On the basis of clinical, neuropsychological, computed tomography, and radionuclidecisternographic findings, they concluded that chronic folate deficiency could induce cerebral atrophy.[11] In general medical patients admitted acutely to hospital, 71% of

those with severe folate deficiency had organic brain syndrome, compared with 31% of a control group.[12] Runcie, who described 10 cases and reviewed the literature, emphasised that the syndrome of folate responsive dementia and depression, sometimes with additional cord or peripheral nerve signs, was much commoner in geriatric and psychogeriatric units than was (or still is) recognised.[13]

## Psychiatric patients

On the basis of serum or red cell assays, folate deficiency has been reported in up to one third of psychiatric outpatients or inpatients, more so in the former.[3 4] Carney and colleagues emphasised the link with depression and "organic" mental change, and a closer association with endogenous than neurotic depression.[14] Depressed patients with folate deficiency had higher depression scores, higher affective morbidity indices, lower Marke-Nyman (drive) scores, and a poorer response to standard treatment with antidepressants.[15] Although folate deficiency is widely regarded as a secondary dietary consequence of psychiatric illness, nutritional studies have not confirmed this view.[3] Poor diet no doubt contributes to some, perhaps many, cases. Other factors are drugs, including antiepileptic drugs; chronic illness; increased demand; and malabsorption, and in some patients the cause is unexplained.

Bottiglieri et al identified a biological subgroup of patients with depression, raised plasma homocysteine concentration, folate deficiency, and impaired monoamine neurotransmitter metabolism.[16] The observation of raised plasma homocysteine in 20-30% of depressed patients is in keeping with the earlier studies of folate concentrations.[3 4]

The few controlled clinical trials of vitamin therapy in addition to standard psychotropic medication have all reported positive effects on patients' mental state. In a double blind placebo controlled trial in depressive patients treated with lithium, the addition of 200 μg of folic acid for one year significantly improved affective morbidity.[17] Similarly, the addition of 500 μg of the vitamin to fluoxitine for 10 weeks significantly improved antidepressant response, especially in women.[18] In a double blind placebo controlled trial Godfrey et al added 15 mg of methylfolate to standard psychotropic medication and reported significant and increasing clinical and social recovery of folate deficient depressed and schizophrenic groups over six months.[19] Earlier Botez et al had reported improvement in both mood and neuropsychological function in a controlled trial of folic acid 15 mg daily alone for four months in depression.[20]

## Geriatric and psychogeriatric patients

The highest incidence of folate deficiency as measured by serum and red cell folate concentrations is in elderly populations, especially psychogeriatric patients.[3] A close association with dementia and depression, apathy, withdrawal, and lack of motivation has been noted.

One reason for the apparently high incidence of folate deficiency in elderly people is that folate concentrations in serum and cerebrospinal fluid fall and plasma homocysteine rises with age, perhaps contributing to the ageing process.[21]

Among 115 admissions to a geriatric unit, 16% had low red cell folate.[22] The 14 patients with dementia had lower folate concentrations than any other diagnostic group and the severity of the dementia on the mental assessment score was significantly correlated with folate concentrations, raising the possibility of an aetiological role. In a case-control study of 164 patients with Alzheimer's disease, cognitive decline was significantly associated with raised plasma homocysteine and lowered serum folate (and vitamin B-12) concentrations.[6]

In a prospective community based study of 370 healthy elderly Swedish subjects, folate or vitamin B-12 deficiency doubled the risk of subsequently developing Alzheimer's disease.[23] Recently the much larger and longer Framlingham community based study confirmed that a raised plasma homocysteine concentration doubled the risk of developing Alzheimer's and non-Alzheimer's dementia.[9]

In open studies Runcie,[13] reviewing his own and others' experience with folic acid, and Brocker et al,[24] who utilised folinic acid in 50 deficient subjects, emphasised the effects of the vitamin on mood and cognitive function: some patients were strikingly transformed into independent, competent people. Furthermore, in a double blind trial for eight weeks in 96 elderly depressed patients with mild to moderate dementia, Passari et al reported that methylfolate 50 mg daily was as effective as the standard antidepressant trazodone 100 mg daily in improving depressive symptoms rated on the Hamilton scale, irrespective of folate status.[25]

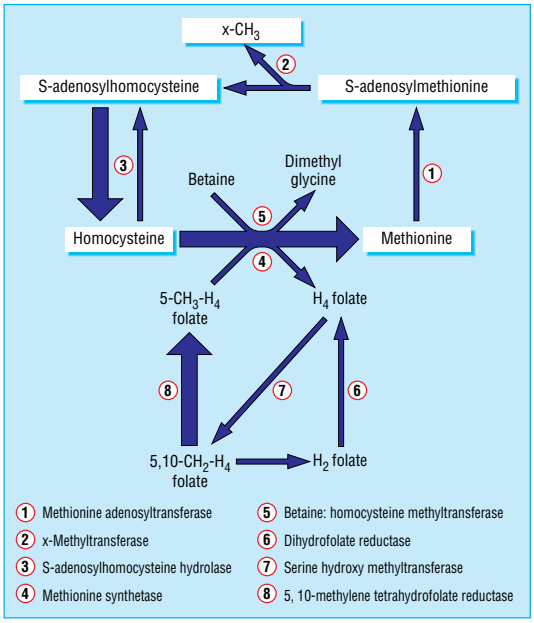
## Neuropsychological studies

In a placebo controlled trial of folic acid 15 mg daily for four months in 24 folate deficient depressed subjects with mild cognitive impairment, Botez et al reported significant improvement in the Wechsler IQ memory scale and Kohs block design test.[20] In an open study of 38 folate deficient elderly subjects with depression, lethargy, and memory impairment, folinic acid 50 mg per week for 120 days significantly improved visuomotor performance, visuospatial memory, logical reasoning, associative memory, and activities for daily living.[26]

In a survey of nutritional status and cognitive functioning in 260 healthy elderly subjects aged 60 to 94 years in the community, there was a significant relation between impaired abstract thinking ability and memory and lower folate levels and intake.[27] In the New Mexico ageing process study of 137 community residents aged 66 to 90 years, weak but significant associations were found between measures of abstract thinking and concentrations of folate (as well as other B vitamins).[28] In the normative ageing study of 70 men aged 54 to 81, Riggs et al found that low serum folate, low vitamin B-12, and especially high plasma homocysteine were significantly associated with impaired spatial copying skills.[29]

In the Kingsholmen ageing and dementia project in Stockholm in 250 old (75 to 96 years) and in 71 very old (90 to 101 years) otherwise healthy subjects in the community, impaired episodic memory was related to

low serum concentrations of vitamin B-12, but more so to low serum concentrations of folate.[30] The selective effects of folate deficiency on episodic memory were suspected to be related to encoding and retrieval mechanisms. Wahlin et al extended their studies of the same populations to include a wider range of cognitive functions—spatial orientation, visuospatial functioning, perceptual motor speed, attention, short term memory, and verbal fluency. They found an overall effect of folate status on cognitive function, whereas the overall effect of vitamin B-12 status did not approach statistical significance, although it added to the effects of reduced folate status. In particular, there were specific effects on visuospatial functioning, cognitive shift and flexibility, attention, working memory, and phonemic search, but only marginal effects on spatial orientation, primary memory, and category fluency. The pattern of cognitive dysfunction is claimed to resemble that in normal ageing—that is, impairment in tasks that involve little structure, are unfamiliar, speeded, and attention demanding and involve complex processing of information.



Inter-relations of folate and methylation cycles

## Neuropathological studies

In the case-control study of Clark et al the diagnosis of Alzheimer's disease was confirmed neuropathologically in 76 patients in whom higher plasma homocysteine was associated with a more rapid atrophy of the medial temporal lobes over a three year period.[6] The authors suspected a toxic microvascular mechanism.[6]

Snowden et al studied prospectively 30 elderly nuns from the same environmental and nutritional background.[8] They died at the mean age of 91 (range 78 to 101) years, and half had neuropathological lesions of Alzheimer's disease. Of 18 nutritional factors examined, only serum folate was significantly negatively 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.

## Neurochemical aspects

Unusually, folic acid in the form of methylfolate is present in cerebrospinal fluid in humans in concentrations three times greater than in serum.[21] The active transport mechanism for methylfolate across the blood-brain barrier strictly limits the entry of the vitamin, perhaps for reasons concerned with the excitatory (convulsant) properties of folic acid.[2 4]

Folates are involved in one-carbon metabolism in the brain as elsewhere. The folate cycle is responsible for the synthesis of methyl groups, which are ultimately utilised by S-adenosyl methionine in innumerable methylation reactions involving nucleoproteins, proteins, membrane phospholipids, neurotransmitters and monoamines. Deficiency of both folic acid and vitamin B-12 will impair methylation processes with the accumulation of homocysteine amongst other effects. The intimate relations of folate, homocysteine and SAM are shown in the figure.

Concentrations of folate in serum and cerebrospinal fluid decline and those of plasma homocysteine rise with age, which contributes to the apparently high incidence of the vitamin deficiency in geriatric and psychogeriatric populations.[3 21] Low concentrations of folate in serum, red cells, and cerebrospinal fluid are associated with depression and dementia in a wide range of clinical neuropsychiatric settings, as is raised plasma homocysteine(see above). There is also increasing evidence of an association between plasma homocysteine and vascular disease, and the increased risk of dementia, including Alzheimer's disease, associated with raised plasma homocysteine may be mediated by a vascular or possibly a neurotoxic mechanism.[6 9] Mood and some cognitive functions may be related to methylation processes in the brain.[31] With respect to depression, this hypothesis is supported by the similar effect of S-adenosylmethionine to that of folates on mood, and by the influence of folates and S-adenosylmethionine on monoamine metabolism, which is also incriminated in depression.[3 31] The lowest concentrations of folate and S-adenosylmethionine in cerebrospinal fluid are found in dementia, including Alzheimer's disease.[32]

## Conclusions

Folates are important in the nervous system at all ages and there is growing evidence of their involvement in the ageing brain, especially in mood and cognitive function.

The association of folate deficiency, as reflected by low concentrations of folate in serum, red cells, and cerebrospinal fluid and raised plasma concentrations of homocysteine, with depression and dementia has been confirmed in epileptic, neurological, psychiatric, geriatric and psychogeriatric patients and is supported by neuropsychological, neuropathological, and neurochemical studies. Some of the deficiency may be related to ageing, some may be secondary to mental illness, and some primary, but whether it is primary or secondary, open and controlled treatment studies confirm an aetiological link with specific effects of the vitamin on mood, drive, initiative, alertness, concentration,

psychomotor speed, and social activity. These observations are reinforced by the cognitive studies in otherwise healthy subjects, suggesting that low folate levels are associated with patterns of impairment also found in ageing.

Within the wide spectrum of depressive disorders, a subgroup has been identified in which folate and related methylation process are involved. With respect to dementia, there is evidence that folate deficiency may contribute to the cognitive impairment of the ageing brain, sometimes leading to reversible dementia but also increasing the risk of Alzheimer's disease and vascular dementia, perhaps by methylation related processes or by homocysteine mediated vascular or neurotoxic mechanisms. It is well known that depression may be a precursor of dementia in a range of neuropsychiatric syndromes.

The diagnosis of folate deficiency still presents problems for physicians and neuropsychiatrists if haematological abnormalities are absent. Some studies suggest that folate deficiency affects the nervous system only at certain not very well defined critically low concentrations of folic acid or high concentrations of homocysteine. This imprecision almost certainly relates to the important influence of duration of deficiency as well as degree of deficiency, in addition to other predisposing factors—for example, genetic factors. Other data, especially in relation to some cognitive impairments in otherwise healthy elderly people in the community, suggest more of a continuum, with folate levels related to performance even within the "normal range." This raises questions about the optimum nutritional environment for the healthy brain, which may not be closely related to arbitrary blood levels.

Clearly, further clinical trials in precisely defined clinical categories are needed, but they should be long term (at least six months to one year) as the impact of folate is slow and cumulative over many months, perhaps because blood-brain barrier mechanisms limit entry to the brain. Small doses over the long term may be preferable to larger doses in the short or long term, not least because of risks to the nervous system, especially in vitamin B-12 deficiency and epilepsy.[4] It is not clear which folate formulation is preferable: folic acid, folinic acid, or perhaps methylfolate (the transport form across the blood-brain barrier). The best way forward may be to undertake large scale community based studies of folate supplementation or food fortification to explore the preventive potential of the vitamin for mood and cognitive disorders. Such studies are being designed or undertaken for the possible prophylaxis of vascular disease and could be adapted to address the question of preventing or reducing depression and dementia, including vascular dementia, while taking into account the special requirements of the nervous system.

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1 Reynolds EH. Mental effects of anticonvulsants, and folic acid metabolism. *Brain* 1968;91:197-214.
2 Botez MI, Reynolds EH, eds. *Folic acid in neurology, psychiatry and internal medicine*. New York: Raven, 1979.
3 Bottiglieri T, Crellin R, Reynolds EH. Folate and neuropsychiatry. In: Bailey LB, ed. *Folate in health and disease*. New York: Marcel Dekker, 1995:435-62.
4 Reynolds EH. Benefits and risks of folic acid to the nervous system. *J Neurol Neurosurg Psychiatry* 2002;72:567-71.
5 Shorvon SD, Carney MWP, Chanarin I, Reynolds EH. The neuropsychiatry of megaloblastic anaemia. *BMJ* 1980;281:1036-42.
6 Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM, et al. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. *Arch Neurol* 1998;55:1449-55.
7 Selhub J, Bagley LC, Miller J, Rosenberg IH. B vitamins, homocysteine and neuro cognitive function in the elderly. *Am J Clin Nutr 2000*;71(suppl):S614-20.
8 Snowdon DA, Tully CL, Smith CD, Riley KP, Markesbery WR. Serum folate and the severity of atrophy of the neocortex in Alzheimer disease: findings from the nun study. *Am J Clin Nutr* 2000;71:993-8.
9 Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenber IH, D'Agostino RB, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med* 2002;346:476-83.
10 Hommes OR, Hollinger JL, Jansen MJT, Schoofs M, Vanderweil T, Kox JCN. Convulsant properties of folate compounds: some considerations and speculations. In: Botez MI, Reynolds EH, eds. *Folic acid in neurology, psychiatry and internal medicine*. New York: Raven, 1979.
11 Botez MI, Fontaine F, Botez T, Bachevalier J. Folate-responsive neurological and mental disorders: report of 16 cases. *Eur Neurol* 1977;16:230-46.
12 Reynolds EH, Rothfeld P, Pincus J. Neurological disease associated with folate deficiency. *BMJ* 1973;ii:398-400.
13 Runcie J. Folate deficiency in the elderly. In: Botez MI, Reynolds EH, eds. *Folic acid in neurology, psychiatry and internal medicine*. New York: Raven, 1979:493-9.
14 Carney MWP, Chary TKN, Laundy M, Bottiglieri T, Chanarin I, Reynolds EH, et al. Red cell folate concentrations in psychiatric patients. *J Affect Disord* 1990:19;207-13.
15 Reynolds EH, Preece JM, Bailey J, Coppen A. Folate deficiency in depressive illness. *Br J Psychiatry* 1970;117:287-92.
16 Bottiglieri T, Laundy M, Crellin R, Toone BK, Carney MWP, Reynolds EH. Homocysteine, folate, methylation and monoamine metabolism in depression. *J Neurol Neurosurg Psychiatry* 2000;69:228-32.
17 Coppen A, Chaudhry S, Swade C. Folic acid enhances lithium prophylaxis. *J Affect Disord* 1986;10:9-13.
18 Coppen A, Bailey J. Enhancement of the antidepressant action of fluoxitine by folic acid: a randomised, placebo controlled trial. *J Affect Disord* 2000;60:121-30.
19 Godfrey PSA, Toone BK, Carney MWP, Flynn TG, Bottiglieri T, Laundy M, et al. Enhancement of recovery from psychiatric illness by methyl folate. *Lancet* 1990;336:392-5.
20 Botez MI, Botez T, Leveille J, Bielmann P, Cadotte M. Neuropsychological correlates of folic acid deficiency: facts and hypotheses. In: Botez MI, Reynolds EH, eds. *Folic acid in neurology, psychiatry and internal medicine*. New York: Raven, 1979:435-61.
21 Bottiglieri T, Reynolds EH, Laundy M. Folate in CSF and age. *J Neurol Neurosurg Psychiatry* 2000;69:562.
22 Sneath P, Chanarin I, Hodkinson HM, McPherson CK, Reynolds EH. Status in a geriatric population and its relation to dementia. *Age Ageing* 1973;2:177-82.
23 Wang H-X, Wahlin A, Basun H, Fastbom J, Winblad B, Frattelioni L. Vitamin B12 and folate in relation to the development of Alzheimer's disease. *Neurology* 2001;56:1188-94.
24 Brocker P, Lebel C, Maurin H, Lods JC. Carences en folates chez les sujets ages: interet de leur correction dans le traitement des troubles du comportement. *Semaine des Hopitaux de Paris* 1986;62:2135-9.
25 Passeri M, Cucinotta D, Abate G, Senin U, Ventura A. Oral 5-methyltetrahydrofolic acid in senile organic mental disorders with depression: results of a double-blind multicenter study. *Aging Clin Exp Res* 1993;5:63-71.
26 Rapin JR, Le Poncin M, Grebyl J. Blood folate deficiencies and cognitive functions in aging. *Trends Biomed Gerontol* 1988;1:221-3.
27 Goodwin JS, Goodwin JM, Garry PJ. Association between nutritional status and cognitive functioning in a healthy elderly population. *JAMA* 1983:249;2917-21.
28 La Rue A, Koehler KM, Wayne SJ, Chiulli SJ, Harland KY, Garry P. Nutritional status and cognitive functioning in a normally aging sample: a six year reassessment. *Am J Clin Nutr* 1997;65:20-9.
29 Riggs KM, Spiro A, Tucker K, Rush D. Relations of vitamin B12, vitamin B6, folate and homocysteine to cognitive performance in the normative aging study. *Am J Clin Nutr* 1996;63:306-14.
30 Wahlin TBR, Wahlin A, Winblad B, Backman L. The influence of serum vitamin B12 and folate status on cognitive functioning in very old age. *Biol Psychol* 2001;56:247-65.
31 Reynolds EH, Carney MWP, Toone BK. Methylation and mood. *Lancet* 1984:ii;196-8.
32 Bottiglieri T, Godfrey P, Flynn T, Carney MWP, Toone BK, Reynolds EH. Cerebrospinal fluid S-adenosylmethionine in depression and dementia: effects of treatment with parenteral and oral S-adenosyl methionine. *J Neurol Neurosurg Psychiatry* 1990:53;1096-8.

*Endpiece*

## What we call luck

What we call luck is the inner man externalised. We make things happen to us.

Robertson Davies (1913-95), *What's bred in the bone*, London: Penguin, 1986