REVIEW ARTICLE

Drugs 48 (2): 137-152, 1994
0012-6667/94/0008-0137/$16.00/0



# The Clinical Potential of Ademetionine (*S*-Adenosylmethionine) in Neurological Disorders

*Teodoro Bottiglieri*,[1] *Keith Hyland*[1] and *Edward H. Reynolds*[2]

1 Metabolic Disease Center, Baylor Research Institute, Dallas, Texas, USA
2 Department of Neurology, Institute of Psychiatry and King's College School of Medicine and Dentistry, London, England

## Contents



## Summary

This review focuses on the biochemical and clinical aspects of methylation in neuropsychiatric disorders and the clinical potential of their treatment with ademetionine (*S*-adenosylmethionine; SAMe). SAMe is required in numerous transmethylation reactions involving nucleic acids, proteins, phospholipids, amines and other neurotransmitters. The synthesis of SAMe is intimately linked with folate and vitamin $B_{12}$ (cyanocobalamin) metabolism, and deficiencies of both these vitamins have been found to reduce CNS SAMe concentrations. Both folate and vitamin $B_{12}$ deficiency may cause similar neurological and psychiatric disturbances including depression, dementia, myelopathy and peripheral neuropathy. SAMe has a variety of pharmacological effects in the CNS, especially on monoamine neurotransmitter metabolism and receptor systems. SAMe has antidepressant properties, and preliminary studies indicate that it may improve cognitive function in patients with dementia. Treatment with methyl donors (betaine, methionine and SAMe) is associated with remyelination in patients with inborn errors of folate and C-1 (one-carbon) metabolism. These studies support a current

theory that impaired methylation may occur by different mechanisms in several neurological and psychiatric disorders.

Ademetionine (*S*-adenosylmethionine; SAMe) is the methyl donor to numerous and diverse acceptor molecules including DNA, proteins, phospholipids and catechol- and indoleamines.[1] Early clinical studies in schizophrenia first directed attention on the relationship between mental illness and methylation in the CNS, where it was thought the *O*-methylation of catecholamines may result in the production of a mescaline-like compound having hallucinogenic properties.[2] Later, studies showed that the administration of methionine (20 g/day), a precursor of SAMe, to schizophrenic patients acutely exacerbated the psychosis in 40% of patients.[3] No abnormal methylated derivatives in urine[4] or cerebrospinal fluid (CSF) were ever identified.[5]

More recent evidence implicates the pathways of methyl carbon metabolism as a probable pathogenic cause for schizophrenia, without invoking an endogenous psychotogen. A deficiency of methionine adenosyltransferase (MAT) has been reported in schizophrenic patients not receiving medication.[6-8] The oxidation of the *S*-methyl carbon of methionine has also been studied by administration of [$^{11}$C]methyl- or [$^{14}$C]methyl-L-methionine and measuring the expired radiolabelled $CO_2$.[9] The rate and total expiration of radiolabelled $CO_2$ was 3 times less in 'unmedicated' schizophrenic patients than in controls, indicating a possible enzymatic defect in the metabolism of methyl groups.

Over the past decade a clearer understanding of the role of methylation in relation to other neurological and psychiatric disorders has emerged. There is an intimate relationship between SAMe, folate and vitamin $B_{12}$ (cyanocobalamin) metabolism (fig. 1). Deficiencies in the latter two can lead to similar neurological and psychiatric complications.[10,11] The most common findings associated with vitamin $B_{12}$ deficiency are peripheral nerve and spinal cord disorders. Psychiatric disorders, mainly depression, are more frequent with folate deficiency; more rarely, spinal cord and peripheral nerve involvement are present. Dementia is equally common in both deficiencies.[12] In several European countries, SAMe has been available as a pharmaceutical preparation for parenteral and oral use.

It is of particular interest that clinical studies have shown SAMe to be effective as an antidepressant. These studies have been the subject of 2 detailed reviews.[13,14] These independent observations of the neuropsychiatric complications of vitamin $B_{12}$ and folate deficiencies and the antidepressant effect of SAMe both emphasise the importance of methylation in the CNS.

In this article we review the neurochemical and neuropharmacological aspects of SAMe, and the neuropsychiatric disorders in which abnormalities of SAMe metabolism have been described. In addition we examine, where appropriate, the clinical potential for pharmacological intervention with SAMe.

## 1. Neurochemical and Neuropharmacological Aspects of Methylation

### 1.1 Ademetionine (*S*-Adenosylmethionine; SAMe) and the Methyl Transfer Pathway

SAMe is formed from the condensation of methionine and adenosine triphosphate (ATP) with the liberation of phosphate and pyrophosphate in a reaction catalysed by ATP:MAT.[15] The daily dietary intake of methionine is not sufficient to supply the total amount required for SAMe synthesis. The additional requirement for methionine is derived from the methylation of homocysteine, which involves 5-methyltetrahydrofolate (5-$CH_3$-$H_4$-folate) [fig. 1], which acts as the methyl group donor in a reaction catalysed by vitamin $B_{12}$–dependent methionine synthetase. An alternative route for the synthesis of methionine involves the vitamin $B_{12}$–independent transfer of a methyl group from betaine to homocysteine in a reaction catalysed by betaine:homocysteine methyltransferase (BHMT)

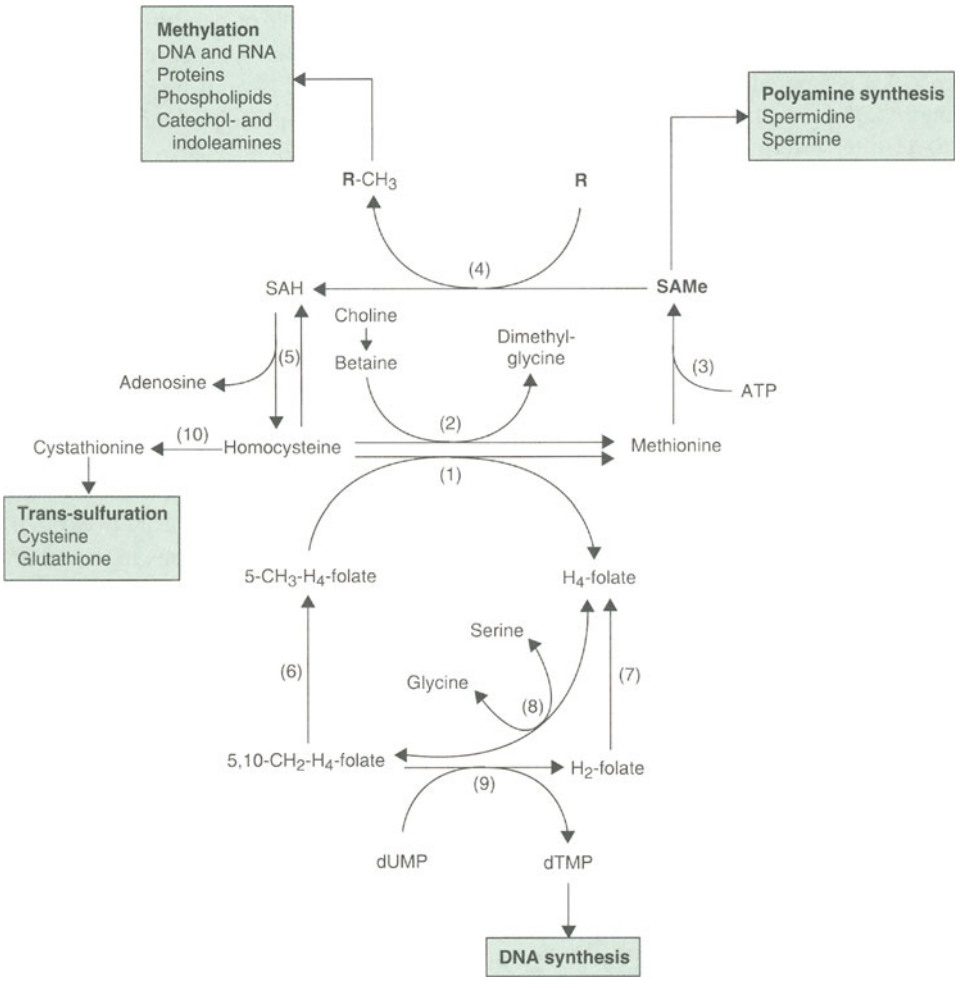


**Fig. 1.** Relationship between the folate one-carbon cycle and ademetionine (*S*-adenosylmethionine) metabolism: (1) methionine synthetase; (2) betaine:homocysteine methyltransferase; (3) methionine adenosyltransferase; (4) R-methyl transferase; (5) SAH hydrolase; (6) 5,10-methylenetetrahydrofolate reductase; (7) dihydrofolate reductase; (8) serine hydroxymethyltransferase; (9) thymidylate synthetase; (10) cystathionine-β synthetase. *Abbreviations:* 5,10-$CH_2$-$H_4$-folate = 5,10-methylenetetrahydrofolate; 5-$CH_3$-$H_4$-folate = 5-methyltetrahydrofolate; dTMP = deoxythymidine monophosphate; dUMP = deoxyuridine monophosphate; $H_2$-folate = dihydrofolate; $H_4$-folate = tetrahydrofolate; SAH = *S*-adenosylhomocysteine; SAMe = ademetionine (*S*-adenosylmethionine).

[fig. 1]. BHMT is absent in CNS tissue from various animal species[16] and human brain tissue.[17] The CNS *de novo* synthesis of methionine is therefore dependent on 5-$CH_3$-$H_4$-folate and vitamin $B_{12}$ metabolism. An impairment of either of these 2 areas of metabolism in animals[18] or humans[19,20] can result in decreased brain or CSF concentrations of SAMe.

SAMe is required in over 35 different methyltransferase reactions,[1] where it donates its methyl group to a large and varied group of acceptor molecules. The demethylated product from all methyltransferase reactions is *S*-adenosylhomocysteine (SAH), which is rapidly metabolised to homocysteine by SAH hydrolase (fig. 1). Under normal physiological conditions this reac-

tion is in favour of homocysteine production; however, if homocysteine accumulates, SAH formation is favoured. SAH is a potent competitive inhibitor of most methylation reactions, and the ratio of SAMe to SAH, often referred to as the methylation ratio or methylation index, is said to regulate the activity of methyltransferase reactions.[21] Inhibition of methyltransferases may therefore arise as a result of SAMe deficiency or SAH accumulation.

Homocysteine is produced entirely from the methylation cycle, as it is totally absent from any dietary source. It is an important branch-point metabolite. It can: (i) determine the direction in which the SAH hydrolase reaction proceeds; (ii) undergo remethylation to methionine; or (iii) undergo condensation with serine to form cystathionine in a reaction catalysed by cystathionine-β synthetase (fig. 1). In the latter reaction, homocysteine is committed to the trans-sulfuration pathway, leading to the formation of glutathione, a major cellular antioxidant.

The main factor which regulates the fate of homocysteine is SAMe. An increase in SAMe concentration inhibits 5,10-methylenetetrahydrofolate reductase, which is the enzyme responsible for the formation of 5-$CH_3$-$H_4$-folate, and stimulates cystathionine-β-synthase.[22] The net effect will be a decrease in the flow through the methionine synthetase pathway and a diversion of homocysteine metabolism towards the trans-sulfuration pathway. This dual regulatory mechanism suggests that normally the steady-state concentrations of the components of the methylation cycle are carefully regulated to maintain levels of SAMe.[23] Disruption of this control mechanism could, therefore, have far reaching effects.

### 1.2 Effects on Monoamine Neurotransmitter Metabolism

The involvement of SAMe in the multitude of methylation reactions points to the possible manipulation of many areas of neurochemistry by pharmacological administration of SAMe. Monoamine neurotransmitters are of particular interest as disturbances in their metabolism have been implicated in a variety of neurological and psychiatric diseases.[24] The antidepressant properties of SAMe have led several investigators to study its influence on monoamine neurotransmitter metabolism. Tyrosine hydroxylase, the rate-limiting enzyme for catecholamine synthesis, can be activated *in vitro* by SAMe, an effect inhibited by SAH.[25] The mechanism of activation by SAMe was reported to be via a decrease in $k_m$ (rate constant) for the pterin cofactor and an increase in protein carboxymethylation.

There is evidence that SAMe increases the turnover of noradrenaline (norepinephrine), serotonin (5-hydroxytryptamine; 5-HT) and dopamine. Algeri et al.[26] showed that SAMe administration caused a rapid and pronounced rise (60 to 90%) in noradrenaline concentrations in the rat brain stem and hypothalamus. In the same study, the conversion of tyrosine to noradrenaline was studied after an intraventricular dose of [$^3$H]*l*-tyrosine. There was a significant increase in the accumulation of the noradrenaline metabolite, 3-methoxy-4-hydroxyphenylglycol, in SAMe-treated animals compared with saline controls.

The administration of SAMe was associated with an increase in serotonin and its metabolite, 5-hydroxyindole acetic acid (5-HIAA), in some brain regions,[27,28] and SAMe treatment enhanced the increase in 5-HIAA which follows reserpine treatment.[27] Furthermore, a single intraperitoneal injection of SAMe increased noradrenaline and dopamine concentrations in the rat brain.[29]

SAMe may affect monoamine reuptake mechanisms. Fonlupt et al.[30] found that SAMe inhibited neuronal high affinity uptake of noradrenaline by a temperature-dependent mechanism which could be reversed by micromolar concentrations of SAH. However, Algeri et al.[26] reported that SAMe had no effect on the uptake of catecholamines or serotonin into isolated cerebral nerve endings, and so does not share an action typical of imipramine-like antidepressants. SAMe has been shown to have some weak and inconsistent actions on monoamine oxidase (MAO) activity, such as an inhibitory ef-

fect on MAO type B in brain[31] or increased MAO activity in heart or brain tissue.[32]

The effect of SAMe administration on neurotransmitter metabolism in humans has been more difficult to assess. The sampling of CSF for the determination of monoamines and their metabolites has been one approach. In a study which measured the accumulation of 5-HIAA and homovanillic acid (HVA) in CSF by using the probenecid test to prevent the egress of acidic metabolites from CSF, SAMe treatment resulted in a significant increase (97%) in 5-HIAA and a nonsignificant increase (57%) in HVA, when compared with those in placebo-treated patients.[33] In a placebo-controlled trial, depressed patients treated parenterally for 14 days with SAMe 200 mg/day showed a significant increase in CSF 5-HIAA concentrations.[34] There was also a highly significant correlation between CSF SAMe and CSF HVA levels in depressed patients treated with SAMe.[35]

### 1.3 Effects on Receptor Systems

Many drugs exert a pharmacological action through their effects on biogenic amine neurotransmitter receptors.[36] SAMe (400mg intravenously) given for 1 week to depressed patients suppressed the orthostatic rise in pulse rate, and in plasma noradrenaline levels, compared with that in placebo recipients.[37] The slowing in pulse rate after SAMe was similar in magnitude to that seen after β-blockers. There is also evidence that SAMe facilitates the mood-elevating action of phenoterole, a β-adrenergic agonist, when given to depressed patients.[38]

Cohen et al.[39] studied the effect of SAMe and other antidepressant treatment on α- and β-adrenoceptors in rat cerebral membranes. After 1 week's treatment with SAMe there was an increase in the density of β-receptors and a decrease in the affinity of α-receptors for phenylephrine. In 30-month-old rats, the binding of the β-adrenergic agonist, [$^3$H]dihydro-alprenolol (DHA), to rat brain membranes was decreased compared with that in young rats (3 months old). Long term treatment of old rats with SAMe was shown to reverse this effect and also decrease the membrane microviscosity.[40] In this study, the binding of the dopamine agonist [$^3$H]spiroperidol was not affected by SAMe. However, dopamine-sensitive adenylate cyclase activity, which was reduced in aged rats, was restored to normal. These effects of SAMe on β-adrenergic receptors are consistent with the earlier findings that an increase in erythrocyte phospholipid methylation increases β-adrenoceptor-adenylate cyclase coupling.[41]

SAMe has also been shown to enhance [$^3$H]diazepam and [$^3$H]γ-aminobutyric acid (GABA) binding to crude synaptic plasma membranes from rat cerebellum. This was associated with increased [$^3$H]methyl group incorporation into membrane phospholipids. Both the binding activities and phospholipid methylation could be inhibited by pretreatment with SAH.[42] In the same study, β-adrenergic binding was again shown to be enhanced upon stimulation of phospholipid methylation with SAMe, whereas [$^3$H]spiroperidol binding was not affected.

The number of muscarinic receptors in the striatum and hippocampus of aged rats is significantly lower in comparison with those in young animals. Treatment of aged rats for 30 days with SAMe restored the number of muscarinic receptors to levels found in the striatum and hippocampus from young animals.[43] The *in vitro* addition of SAMe to hippocampal membranes from aged rats resulted in a significant increase in the number of muscarinic binding sites, an effect that was antagonised by coadministration of SAH. The study authors concluded that the reduction in muscarinic receptor density could be related to a decrease in neuronal membrane fluidity induced by aging, and that the increase after SAMe treatment may be due to an increase in the fluidity of cell membranes by stimulating phospholipid synthesis.

The number of prolactin receptors in the hypothalamus and substantia nigra of aged rabbits is significantly lower than the number in young animals. Long term administration of SAMe to aged rabbits restored the number of prolactin binding sites in these brain regions to the amount found in

**Table I.** Studies of cerebrospinal (CSF) ademetionine (*S*-adenosylmethionine; SAMe) in neurological and psychiatric disorders, and in patients with inborn errors of metabolism

| Disorder | CSF SAMe level | No. of patients | Reference |
|---|---|---|---|
| **Psychiatric disorders** | | | |
| Depression | Low | 35 | 65 |
| **Neurological disorders** | | | |
| Parkinson's disease | Low | 23 | 50 |
| Multiple sclerosis | Normal | 16 | 65 |
| Alzheimer's dementia | Low | 10 | 65 |
| SACD[a] | Low | 3 | 98 |
| HIV-related neurological complications | Low | 6 | 48 |
| | Low | 20 | 47 |
| | Low | 16 | 113 |
| **Metabolic defects** | | | |
| 5,10-methylenetetrahydrofolate reductase deficiency | Low | 4 | 19 |
| | Low | 4 | 20 |
| Cbl G defect | Low | 1 | 20 |
| Cbl C & D defect | Low | 2 | 20 |
| MAT II deficiency[b] | Low | 1 | 20 |
| Aromatic amino acid decarboxylase deficiency | Low | 2 | 49 |

a SACD due to vitamin $B_{12}$ deficiency in 2 patients and folate deficiency in 1 patient.

b Presumed MAT II deficiency on the basis of metabolite studies.

*Abbreviations:* Cbl = cobalamin; MAT = methionine adenosyltransferase; SACD = subacute combined degeneration of the spinal cord.

young animals.[44] This effect was also produced *in vitro* with hypothalamic membranes, and again shown to be antagonised by SAH.

## 2. Studies of SAMe and Methyl Donors in Neurological Disorders

There are several reports of changes in SAMe concentrations in the CNS of patients with neuropsychiatric diseases. These are summarised in table I. The effects may be related to drug therapy, as is the case in Parkinson's disease,[45,46] or may be related to an as yet unknown mechanism, as is the case in HIV infection.[47,48] Studies of the use of SAMe in various neurological disorders are summarised in table II. These are discussed in greater detail in the following sections.

### 2.1 Parkinson's Disease

Levodopa is the mainstay of the treatment of Parkinson's disease. Experimental studies in animals have demonstrated that short or long term administration of levodopa lowers brain SAMe.[45] Similar observations in children with neurotransmitter deficiencies treated long term with levodopa have shown that SAMe levels are reduced by 22 to 40% versus pretreatment values.[46] Reduced CSF SAMe concentrations have been reported in 2 children with aromatic *l*-amino acid decarboxylase (AADC) deficiency, resulting in an accumulation of endogenous levodopa.[49]

The fall of SAMe concentrations occurs because levodopa acts as a potent methyl acceptor, being rapidly converted to 3-*O*-methyldopa. There are no studies of CSF SAMe in patients with Parkinson's disease treated with levodopa. However, CSF SAMe concentrations have been reported to be significantly reduced in untreated idiopathic Parkinsonian patients.[50] The aetiology of this observation is not known, and further studies are required to verify this report.

The biochemical and neurological consequences of a long term reduction of CNS SAMe concentrations in Parkinsonian patients are not known. Depression is probably the most common mental disturbance in Parkinson's disease.[51] In a review of 14 studies that involved 1500 patients, the mean prevalence of depression in Parkinson's disease was 46%. It is generally accepted that the aetiology of some depressive illness involves disturbance in serotonin metabolism,[52,53] and there is much evidence to show that serotonin metabolism is also impaired in Parkinson's disease.[53-56] Treatment of Parkinson's disease with levodopa has been implicated both as the cause of depression and also as causing a worsening of symptoms in patients who were depressed before the onset of Parkinson's disease.[57,58] The direct inhibition of tryptophan hydroxylase by levodopa may provide an explanation for these observations,[59] but alternatively, a reduction in brain SAMe concentration may be involved.

There is a substantial body of evidence to show that SAMe acts as a therapeutic agent for the treatment of depression.[13,14] That SAMe also acts as an antidepressant in Parkinson's disease was shown recently in a double-blind crossover study versus placebo. SAMe 400mg orally twice daily plus 200mg intramuscularly daily for 30 days led to a significant improvement in the Hamilton rating scale for depression, compared with placebo. SAMe did not affect the motor component of the disease, nor did it have major adverse effects.[60] It is interesting to note that coadministration of SAMe did not necessitate alteration in levodopa therapy.

Parkinson's disease is a condition in which there may be great potential for SAMe therapy. Further studies are needed to confirm this in patients with Parkinson's disease with or without depression.

### 2.2 Dementia

Reduced levels of folate and vitamin $B_{12}$ are commonly associated with dementia. Crellin et al.[61] have recently reviewed studies of folate deficiency in geriatric and psychogeriatric patients. These studies have revealed at least an 18% incidence of low serum folate levels, increasing to rates as high as 80 to 90% in older psychogeriatric patients. In both geriatric and psychogeriatric patients, dementia is the most common association with folate deficiency.

Shorvon and coworkers[12] compared the neuropsychiatric associations of megaloblastic anaemia due to folate deficiency or vitamin $B_{12}$ deficiency in 50 patients. Two-thirds of both series of patients had nervous system disorders. In both groups, 25% had organic mental change or dementia. Several recent studies have indicated that pa-

**Table II.** Studies of ademetionine (*S*-adenosylmethionine; SAMe) treatment in neurological disorders

| Disorder | No. of patients | Study design | Dosage (mg) and route | Duration | Clinical outcome | Reference |
|---|---|---|---|---|---|---|
| Parkinson's disease | 21 | db, pc | 400 bid PO + 200 IM od | 30 days | Significant improvement in Hamilton and Beck rating scales. No change in Parkinsonian symptoms or change in concomitant levodopa treatment | 60 |
| Alzheimer's dementia | 2 | nc | 400 tid PO | 3-5 months | Both studies showed improved measures of cognitive function, mood and speed of mental processing | 66, 67 |
| | 5 | db, pc | 400 tid PO | 3-5 months | | |
| | 4 | nc | 400 IV od | 14 days | No improvement or worsening of cognitive function or mental state. Significant increase in red blood cell membrane fluidity | 68 |
| Epilepsy | 3 | nc | 200 IV od | 3-14 days | Both studies showed positive response on mood and arousal. No adverse effect on seizure frequency | 67, 75 |
| | 4 | sb, pc | 200 IV od | 8-14 days | | |
| AIDS | 16 | nc | 800 IV od | 14 days | No post-treatment neurological evaluation performed. Significant increase in post-treatment CSF SAMe concentrations | 113 |
| MAT II deficiency | 1 | | 400 tid PO | 12 months | 11-year-old female patient. Pretreatment status showed evidence of demyelination and basal ganglia calcification. MRI evidence of remyelination after SAMe treatment | 20 |

*Abbreviations:* bid = twice daily; CSF = cerebrospinal fluid; db = double-blind; IM = intramuscular; IV = intravenous; MAT = methionine adenosyltransferase; MRI = magnetic resonance imaging; nc = noncomparative; od = daily; pc = placebo-controlled; PO = oral; sb = single-blind; tid = 3 times daily.

tients with Alzheimer's dementia have either low serum[62] or low CSF vitamin $B_{12}$.[63,64]

The cause of the folate and vitamin $B_{12}$ deficiencies in many of the above mentioned studies is unclear. Nutritional intake was not thoroughly investigated, and it is quite probable that secondary dietary deficiency may be involved. Whatever the cause of the folate or vitamin $B_{12}$ deficiency, a probable impairment in CNS SAMe metabolism and methylation may occur.

It is interesting to note that CSF SAMe concentrations have been shown to be significantly reduced (41%) in patients with Alzheimer's dementia,[65] and that the administration of oral SAMe for 3 to 5 months (400mg 3 times daily) increased plasma and CSF SAMe concentrations,[65] and improved measures of cognitive function as well as mood and speed of mental processing.[66,67] Cohen et al.[68] have also studied the effects of SAMe administration on 4 patients with Alzheimer's dementia. These patients received SAMe 200 or 400mg daily intravenously for 14 days. Although there were no changes in cognitive function or mood state, attributed to the short duration of the study, the authors did find a significant increase in red cell membrane fluidity associated with an increase in phospholipid methylation.

Patients with Down's syndrome also develop an Alzheimer's dementia–like neuropathology and eventually a clinical dementia syndrome.[69] Low red cell folate and macrocytosis are commonly associated with this disorder, and the incidence of macrocytosis correlates with intellectual decline.[70,71] Lymphocytes from patients with Down's syndrome are also more sensitive to methotrexate toxicity than are control individuals, suggesting altered folate metabolism.[72]

The gene encoding for cystathionine-β synthetase, the enzyme that converts homocysteine to cystathionine, is localised on chromosome 21. Altered folate and C-1 (one-carbon) metabolism may be due to the considerable increase in cystathionine-β synthetase activity that has been reported in cultured fibroblasts from patients with Down's syndrome.[73] As a result, plasma homocysteine levels are lower,[74] and less may be available for the synthesis of methionine, SAMe and the recycling of C-1 units through the folate cycle. These studies demonstrating folate and vitamin $B_{12}$ deficiency in some patients with dementia, and other diseases affecting cognitive function, indicate that abnormal methylation may be involved in the pathogenesis of the dementia in these cases.

### 2.3 Epilepsy

Phenytoin and barbiturates lead to a decrease in serum, red blood cell and CSF folate in a high proportion of epileptic patients.[11] There is an association between the drug-induced folate deficiency and mental disorders in epileptic patients, especially depression and dementia.[11,75] Reynolds[76] treated 26 folate-deficient epileptic outpatients with folic acid for 1 year, and reported a consistent pattern of mental improvement in 22 patients. The main effect was on drive, mood, initiative, motivation, alertness and sociability.

Recent studies, one in children,[77] two in adults[78,79] and one in the community,[80] have all emphasised a close relationship between folate deficiency and mood disorders in epilepsy.

In a pilot noncomparative study of parenteral SAMe 200 mg/day to 3 patients with long-standing chronic partial seizures, who were either withdrawn or depressed, a positive response on mood or arousal was noted within 3 to 4 days.[67,75] In a single-blind study comparing intravenous SAMe 200 mg/day against placebo for 8 to 14 days in 4 additional patients with chronic epilepsy, a similar effect on mental function was noted in 2 patients.[67,75] In these few patients, SAMe had no adverse effect on seizure frequency, unlike folate which can aggravate seizure control in some patients[76,81] and in experimental models.[82,83]

Longer term studies with the newly available oral SAMe would be of interest in epileptic patients with and without mood disturbances, and also with and without drug-induced folate deficiency.

### 2.4 Multiple Sclerosis

Recent reports of an association between multiple sclerosis and vitamin $B_{12}$ deficiency have revived interest in this area. Nijst et al.[64] have reported a significant lowering of CSF vitamin $B_{12}$ in this disorder. In a prospective study of 29 patients, Reynolds et al.[84] found significantly lower serum vitamin $B_{12}$ values and increased levels of plasma unsaturated R-binder, a vitamin $B_{12}$–binding protein. Abnormal gel filtration profiles of vitamin $B_{12}$–binding proteins in 4 multiple sclerosis patients suggested an impairment in vitamin $B_{12}$ transport (Bottiglieri, unpublished observations). Additional evidence that vitamin $B_{12}$ deficiency may be associated with multiple sclerosis is indicated in the degree of macrocytosis that has been reported in 2 studies.[85,86]

The majority of patients with multiple sclerosis do not have vitamin $B_{12}$ deficiency, but there is evidence of an overlap of the 2 disorders. The similarities between multiple sclerosis and pernicious anaemia in the gender, racial and geographical distributions are remarkable. Epidemiological studies have shown that in both disorders there is a higher prevalence from the north to south of the UK, and a higher incidence in White than Black North Americans.[87] The female to male ratio in both disorders is 1.3 : 1. As Reynolds[88] has suggested, there may be an increased association between 2 autoimmune or genetically linked disorders. The question arises whether the associated vitamin $B_{12}$ deficiency from any cause is aggravating the underlying multiple sclerosis or hindering the process of remyelination. Vitamin $B_{12}$ deficiency can impair SAMe metabolism and methylation reactions that may play a role in this process. Bottiglieri et al.[65] have studied 16 patients with acute and chronic multiple sclerosis and could not find any significant changes in CSF SAMe, although some patients had the highest values recorded when compared with other neurological control and disease groups.

### 2.5 Subacute Combined Degeneration of the Spinal Cord

Subacute combined degeneration of the spinal cord (SACD) is a disorder characterised by vacuolar myelopathic lesions originating in the posterior and lateral columns of the thoracic cord, progressing to higher regions of the CNS. Although this disorder was thought to be associated only with vitamin $B_{12}$ deficiency, several reports have shown it to be a feature of severe folate deficiency.[20,89,90]

The exact biochemical lesion responsible for the myelopathic lesion in SACD is not yet known, although the evidence suggests that a defect in methylation is a probable cause. Early studies showed that mice treated with cycloleucine, an inhibitor of MAT (and therefore SAMe synthesis), produced a vacuolar demyelination in the spinal cord histologically similar to the SACD found in humans.[91,92]

More recently, a re-investigation of the effect of cycloleucine in young mice has confirmed the early observations and shown that intramyelinic vacuolation in the white matter of brain and spinal cord occurs within 12 hours after a single intraperitoneal dose (2 mg/g), as well as axonal lesions occurring in distal parts of motor nerves resulting in degeneration of intramuscular nerve fibres.[93] In adult mice treated with cycloleucine, the pathology consisted of distal axonal degeneration developing within 1 to 2 days, with little or no intramyelinic vacuolation in the white matter. In these studies, brain SAMe concentrations decreased to 60% of normal within the first 24 hours after administration of cycloleucine.[93] The histopathological effects of cycloleucine were considered to be the result of SAMe deficiency impairing methylation processes known to be important for the stabilisation of myelin through the methylation of myelin basic protein or membrane phospholipids.

Other investigators have used nitrous oxide ($N_2O$), which inactivates the enzyme methionine synthetase as an animal model of SACD. $N_2O$ exposure in the monkey,[94] the fruit bat[95] and the

pig[18] produced a myelopathy similar to that seen in SACD. The supplementation of methionine in the diet significantly ameliorated the $N_2O$-induced neurological lesion in all 3 animal species. These findings suggest that deficiency of either methionine or SAMe could lead to the neurological lesion in SACD. In the $N_2O$-exposed pigs showing signs of neurological impairment, only small nonsignificant decreases in SAMe were reported in the spinal cord and cortex, although there was a significant 30% decrease in the cerebellum.[96] In the same study, substantial increases in SAH in the spinal cord, cortex and cerebellum were found. The raised SAH concentrations resulted in a marked decrease in the SAMe/SAH methylation ratio. Supplementation with methionine increased the CNS SAMe concentrations, thereby normalising the methylation ratio and providing protection against demyelination.[18] These observations could not be replicated in the fruit bat, which is another animal model of SACD.[97]

In humans, CSF SAMe concentrations have been reported to be reduced in an adult with SACD due to folate deficiency[90] and in 2 adults with vitamin $B_{12}$ deficiency.[98] There are no reports of CSF SAH concentrations in patients with SACD.

SACD due to folate and vitamin $B_{12}$ deficiency is fortunately fairly uncommon today, due to modern methods for the detection of these deficiencies. Consequently, patients are diagnosed early before spinal cord involvement has occurred. Treatment with the appropriate vitamin, if given in time, usually results in a complete recovery. In view of the pathological mechanism involved in SACD, treatment with SAMe may have a therapeutic effect in these patients. It would be unethical to substitute a known treatment for one which may have clinical potential in such patients. However, in those that fail to respond to the appropriate vitamin, the use of intensive parenteral or oral SAMe should be considered.

### 2.6 Methotrexate Encephalopathy

Methotrexate is widely used for the treatment of lymphoreticular and other malignancies, including metastatic and recurrent primary brain tumours. Its efficacy is limited by the relatively high incidence of neurological complications. Long term intrathecal, intraventricular or high dose systemic methotrexate therapy, especially in combination with radiation therapy, can lead to a progressive neurological disorder characterised by dementia, seizures, focal motor or visual deficit and coma. The neuropathological findings generally consist of diffuse, bilateral necrotising lesions and astrogliosis in pereventricular white matter with or without calcification.[99,100] A subacute necrotising leucomyelopathy of the spinal cord may also be found, similar to the findings in the white matter of the brain.

Clinical neurological similarities between children treated with methotrexate and those with acquired or inborn errors of folate metabolism have been reported (see section 2.8). This is not surprising, as methotrexate is an antifolate agent, causing inhibition of dihydrofolate reductase (DHFR) and a functional deficiency of reduced folate cofactors. Long term administration to monkeys of intramuscular methotrexate 2 mg/kg weekly for 1 year, a value equivalent to a child's dose on a 'standard' acute lymphoblastic leukaemia (ALL) therapy protocol, resulted in significant decreases in folate content of the liver, kidney, testes and brain.[101] Brain tissue showed the greatest loss; approximately a 90% depletion of folate.

The mechanism(s) by which methotrexate causes a leucoencephalopathy has not yet been elucidated. Surtees and coworkers (personal communication) have studied the effect of a standard treatment regime of intrathecal methotrexate on CSF 5-$CH_3$-$H_4$-folate and SAMe concentrations in 15 children with ALL. After 1 week, the mean CSF 5-$CH_3$-$H_4$-folate concentration was significantly reduced to 18% of the pretreatment value, and after 1 month of therapy, CSF SAMe was significantly reduced to 51% of the pretreatment value. Animal studies have shown that methotrexate treatment can decrease SAMe and increase SAH in rat liver.[102]

In view of the evidence on the role of methylation in the maintenance of myelin formation, it is highly probable that a CNS deficiency of SAMe and/or accumulation of SAH after methotrexate therapy may be responsible for some of the neurological complications. If the neurotoxic (SAMe deficiency and/or SAH accumulation) and antineoplastic (anti-DHFR) effects of methotrexate are due to different mechanisms, then this would potentially allow for an increase in methotrexate efficacy by circumventing neurotoxicity through pharmacological manipulation. Clinical studies involving the use of betaine, methionine or SAMe, in combination with methotrexate, may prove to be effective in the treatment of neurological complications and allow greater tolerance to the antineoplastic therapy.

### 2.7 AIDS-Dementia Complex/HIV Encephalopathy

Neurological complications are frequently found to occur in patients with HIV infection. The most common and intriguing disorder is the development of an AIDS-dementia complex (ADC). ADC was clinically recognised early in the AIDS epidemic, and various terms have since been used to describe this syndrome, including subacute encephalitis, subacute encephalopathy, HIV dementia and HIV encephalopathy. The diversity in terminology has arisen because ADC is really a cohesive constellation of symptoms and signs rather than a single disease entity.

ADC presents as a 'subcortical dementia' with a characteristic cognitive impairment, which may be accompanied by motor and behavioural dysfunction.[103,104] The neuropathology of ADC includes at least 3 overlapping major abnormalities: (i) central gliosis and white matter pallor; (ii) multinucelated encephalitis; and (iii) vacuolar myelopathy.[105-107] The vacuolar myelopathy, which is more common in the later stages of the disease, bears a striking histological resemblance to the SACD that accompanies vitamin $B_{12}$ and folate deficiency.[108,109] ADC is clinically evident in 30% of HIV-infected patients, with about half developing a myelopathy,[103,110] although postmortem examination of brains from patients with AIDS has revealed abnormalities in up to 88% of cases.[111,112]

The similarity in the vacuolar myelopathy seen in patients infected with HIV and patients with vitamin $B_{12}$ or folate deficiency is of particular interest, as disturbances in the folate C-1 cycle and SAMe methylation pathway have been reported in both conditions. Thus, Surtees et al.[48] reported that in 6 children with neurological complications due to HIV infection, CSF concentrations of 5-$CH_3$-$H_4$-folate were low in all the patients studied, and CSF SAMe was low in 5 patients. The cause of the low CSF 5-$CH_3$-$H_4$-folate and SAMe was not known, although a postulated mechanism was the inhibition of folate metabolism by neopterins, which are released following macrophage activation by interferon-$\gamma$.

CSF SAMe and SAH concentrations were examined in 20 HIV-infected adults with and without overt clinical signs of a myelopathy, and in 30 control patients with no neurological complications.[47] All the HIV patients had a normal vitamin $B_{12}$ and folate status. The mean CSF SAMe concentration was significantly lower and the mean CSF SAH concentration significantly higher in the HIV-infected group versus the control group. This resulted in an overall highly significant decrease in the CSF SAMe/SAH methylation ratio, postulated to lead to the inhibition of methylation reactions in the CNS.

In a more recent study, CSF SAMe concentrations were reduced in a group of 16 HIV-infected adults with neurological complications in comparison to a group of 20 surgical control patients.[113] In this study, the integrity of the blood-brain barrier in HIV-infected patients was evaluated and found to be preserved. Seven of the patients were treated with parenteral SAMe butanesulfonate 800 mg/day for 14 days, leading to significant post-treatment increases in CSF SAMe.

An important question in the pathogenesis of the CNS damage seen in AIDS is whether HIV infection in brain macrophages induces disease or

whether CNS disease is part of a broader metabolic disturbance. Current theories of HIV-related CNS dysfunction include involvement of opportunistic infection and toxicity related to cytokine secretion. Alternatively, a disturbance in SAMe and/or SAH metabolism in HIV-infected patients, who may develop a myelopathy similar to SACD due to vitamin $B_{12}$ and folate deficiencies, suggests a common pathogenic mechanism, namely inhibition of CNS methylation processes. It is interesting that patients infected with HIV are more sensitive to the toxic effects of DHFR inhibitors;[114,115] additional evidence that the C-1 folate/SAMe methylation cycle may be perturbed. Clinical trials of SAMe in HIV-infected patients to examine its potential in protecting against the development of a myelopathy and/or other neurological complications, particularly cognitive impairment and depressive symptoms, would be of interest to clarify the role of SAMe and methylation in this disorder.

### 2.8 Inborn Errors of Metabolism Affecting the Methyl Transfer Pathway

Congenital metabolic defects of folate and vitamin $B_{12}$ metabolism have provided a rare opportunity to examine closely the pathological and biochemical consequences of a block in a particular pathway, and have provided substantial evidence to support a role for SAMe and methylation in the maintenance of myelin. 5,10-methylenetetrahydrofolate reductase deficiency results in the inability to form 5-$CH_3$-$H_4$-folate and consequently a defect in the methylation of homocysteine to methionine. Children with this disorder often present early in life with severe and progressive disease of the CNS and a pathology indistinguishable from SACD of the spinal cord.

Hyland et al.[19] first described a 2-year-old girl with 5,10-methylenetetrahydrofolate reductase deficiency who had SACD and a diffuse leucoencephalopathy (confirmed at necropsy), with undetectable concentrations of CSF methionine and SAMe. In 3 other cases, treatment with betaine, which provides an alternative source of methyl groups for the methylation of homocysteine, halted the neurological deterioration and restored the CSF SAMe concentration to within normal limits.[19]

Surtees et al.[20] later described 4 additional cases. In an 18-month-old girl, magnetic resonance imaging (MRI) indicated widespread white matter hypodensities and cerebral atrophy. Biochemical analysis of her CSF showed subnormal concentrations of 5-$CH_3$-$H_4$-folate, methionine and SAMe. MRI examination after treatment with betaine for 12 months showed evidence of remyelination associated with an increase in CSF methionine and SAMe concentrations. The other 3 patients were aged less than 1 year and were too young for MRI assessment of myelination; however, CSF analysis again demonstrated low concentrations of methionine and SAMe. These investigators also studied a 3-year-old child with a cobalamin G defect, causing methionine synthetase deficiency. MRI examination before treatment showed an abnormal signal throughout the deep white matter, consistent with demyelination. CSF methionine and SAMe concentrations were well below the normal range. After 6 months of treatment with methionine, which bypasses the metabolic block, there was MRI evidence for extensive remyelination, and CSF methionine and SAMe were increased to within the reference range.[20]

Evidence that it is SAMe and not methionine that is required for myelin maintenance has come from the study of an 11-year-old patient presumed to have a CNS MAT deficiency.[20] Before treatment, CSF methionine was grossly elevated, CSF SAMe was greatly decreased and there was MRI evidence of demyelination and basal ganglia calcification. Treatment with oral SAMe toluene sulfonate 400mg twice daily for 12 months decreased CSF methionine concentrations and increased CSF SAMe concentrations. MRI examination showed evidence of remyelination.

In all these cases of inborn errors of metabolism affecting the methyltransfer pathway, a deficiency of CSF SAMe was the single consistent biochemical observation that was associated with demyelination. In all cases, except for the patient with presumed MAT deficiency, SAH would be ex-

pected to accumulate and inhibit methylation reactions. In the patient with presumed MAT deficiency, SAH would not be expected to accumulate, which may explain the later onset of her neurological symptoms.[20]

## 3. Conclusions

Methyl group deficiency has been implicated as a pathogenic mechanism in various neuropsychiatric illnesses such as depression, dementia, Parkinson's disease, and some disorders in which demyelination occurs, e.g. SACD, inborn errors of metabolism and AIDS-related myelopathy. Much of the evidence for a role of methylation in CNS function has come from studies on the neuropsychiatry of folate and vitamin $B_{12}$ deficiencies. These deficiencies can cause a methyl group deficiency in the CNS, indicated by reduced concentrations of either 5-$CH_3$-$H_4$-folate or SAMe. In some instances, CSF SAMe may be low in the absence of these deficiencies e.g. HIV infection.

The therapeutic effect of SAMe in some depressive illnesses has led to new nontoxic treatment strategies. There have been encouraging pilot studies of the use of SAMe in patients with Parkinson's disease, epilepsy and Alzheimer's dementia. Furthermore, impaired C-1 metabolism and SAMe synthesis has been proposed to be a common pathogenic mechanism in Alzheimer's dementia, Down's syndrome and HIV infection, thus lending further support for clinical trials with methyl donors in these conditions. Convincing evidence from studies of inborn errors of methyl group metabolism have shown that methylation is important in maintaining the integrity of the myelin sheath. Correction of the methyl group deficiency with methyl group donors, including oral SAMe treatment, can halt or even reverse the demyelination process.

SAMe appears to influence monoamine neurotransmitter metabolism and receptors, which may be the putative mechanism of action in the treatment of depression. Clinical trials to date with SAMe have shown it to be a relatively safe compound, with no serious adverse reactions observed, and it is devoid of any hepatotoxic effects. This is probably related to the fact that it is a natural ubiquitous metabolite present in all organisms. The full clinical potential of SAMe in some neurological disorders remains to be explored.

## References


1. Mudd SH, Cantoni GL. Biological transmethylation methyl-group neogenesis and other one carbon metabolic reactions dependant upon tetrahydofolic acid. In: Florkin M, Stotz EH, editors. Comprehensive biochemistry. Vol. 15. Amsterdam: Elsevier, 1964: 147
2. Smthyies JR. Recent advances in the biochemistry of psychosis. Lancet 1960; 2: 1287-9
3. Cohen S, Nichols A, Wyatt R. The administration of methionine to chronic schizophrenic patients: a review of ten studies. Biol Psychiatry 1974; 8: 209-25
4. Checkley SA, Oon MCH, Rodnight R, et al. Urinary excretion of dimethyltryptamine in liver disease. Am J Psychiatry 1979; 135: 439-41
5. Smthyies JR, Morin RD, Brown GB. Identification of dimethyltryptamine and O-methylbufotenin in human cerebrospinal fluid by combined gas chromatography/mass spectrometry. Biol Psychiatry 1979; 14: 549-56
6. Levi RN, Waxman S. Schizophrenia, epilepsy, cancer, methionine, and folate metabolism: pathogenesis of schizophrenia. Lancet 1975; 2: 11-3
7. Smythies JR. The transmethylation and one-carbon cycle hypothesis of schizophrenia. Psychol Med 1983; 13: 711-14
8. Tolbert LC, Monti JA, O'Shields H, et al. Defects in transmethylation and membrane lipids in schizophrenia. Psychopharmacol Bull 1983; 19: 594-9
9. Sargent T, Kusubov N, Taylor SE, et al. Tracer kinetic evidence for abnormal methyl metabolism in schizophrenia. Biol Psychiatry 1992; 32: 1078-90
10. Botez MI, Reynolds EH, editors. Folic acid in neurology, psychiatry and internal medicine. New York: Raven Press, 1979
11. Reynolds EH. Neurological aspects of folate and vitamin B12 metabolism. Clin Haematol 1976; 5: 661-96
12. Shorvon SD, Carney MWP, Chanarin I, et al. The neuropsychiatry of megaloblastic anaemia. BMJ 1980; 281: 1036-42
13. Janicak PG, Lipinski J, Davis JM. S-adenosylmethionine in depression: a literature review and preliminary report. Alabama J Med Sci 1988; 25: 306-13
14. Friedel HA, Goa KL, Benfield P. S-adenosyl-L -Methionine: a review of its therapeutic potential in liver dysfunction and affective disorders in relation to its physiological role in cell metabolism. Drugs 1989; 38: 389-416
15. Cantoni GL. S-adenosylmethionine; a new intermediate formed enzymatically from L-methionine and adenosinetriphosphate. J Biol Chem 1953; 204: 403-16
16. Finkelstein JD, Kyle WE, Martin J, et al. Activation of cystathionine synthase by adenosylmethionine and adenosylethionine. Biochem Biophys Res Commun 1975; 66; 81-7
17. Mckeever MP, Molloy AM, Weir DG, et al. Betaine-homocysteine methyltransferase: organ distribution in man, pig and rat and subcellular distribution in the rat. Clin Sci 1991; 81: 551-6
18. Weir DG, Keating JN, McParhin J, et al. Methylation deficiency causes vitamin B12 associated neuropathy in the pig. J Neurochem 1988; 51: 1949-52

19. Hyland K, Smith I, Bottiglieri T, et al. Demyelination and decreased S-adenosylmethionine in 5,10-methylentetrahydrfolate reductase deficiency. Neurol 1988; 38: 459-62
20. Surtees R, Leonard J, Austin S. Association of demyelination with deficiency of cerebrospinal fluid S-adenosylmethionine in inborn errors of methyl-transfer pathway. Lancet 1991; 338: 1550-4
21. Cantoni GL. The centrality of S-adenosylhomocysteine in the regulation of the biological utilization of S-adenosylmethionine. In: Borchardt C, Ueland PM, editors. Biological methylation and drug design: experimental and clinical roles of SAM. Clifton: Humana Press Inc., 1986: 227-37
22. Kutzbach C, Stokstad ELR. Mammalian methylenetetrahydrofolate reductase: partial purification properties, and inhibition by S-adenosylmethionine. Biochim Biophys Acta 1971; 250: 459-77
23. Selhub J, Miller JW. The pathogenesis of homocysteine: interruption of the coordinate regulation by S-adenosylmethionine of the remethylation and transsulfuration of homocysteine. Am J Clin Nutr 1992; 55: 131-8
24. Wood JH. Neurobiology of CSF. New York: Plenum Press, 1980
25. Mann S, Hill MW. Activation and inactivation of striatal tyrosine hydroxylase: the effects of PH, ATP, and cyclic AMP, S-adenosylmethionine and S-adenosylhomocystene. Biochem Pharmocol 1983; 32: 3369-74
26. Algeri S, Catto E, Curico M, et al. Changes in rat brain noradrenaline and serotonin metabolism after administration of S-adenosylmethionine. In: Zappia V, Usdin E, Salvatore S, editors. Biochemical and pharmacological roles of adenosylmethionine and the central nervous system. New York: Pergamon Press, 1979: 81-7
27. Curico M, Catto E, Stramentinoli G, et al. Effect of SAMe on 5HT metabolism in rat brain. Prog Neuropysychopharmacol 1978; 2: 65-71
28. Otero-Losada ME, Rubio MC. Acute changes in 5HT metabolism after S-adenosylmethionine administration. Gen Pharmacol 1989; 20: 403-6
29. Otero-Losada ME, Rubio MC. Acute effects of S-adenosylmethionine on catecholaminergic central function. Eur J Pharmacol 1990; 163: 353-6
30. Fonlupt P, Roy C, Pacheco H. Phospholipid methylation and noradrenaline exchanges in a synatosomal preparation from the rat brain. J Neurochem 1982; 38: 1615-20
31. Schatz RA, Stramentinoli G, Sellinger OZ. Decreased cerebral catabolism of [3H]histamine in vivo after S-adenosylmethionine administration. J Pharmacol Exp Ther 1981; 216: 118-24
32. Bidard JN, Darmenton P, Cronenberger L, et al. Effet de la S-adenosyl-L-methionine sur le catabolisme de la dopamine. J Pharmacol 1977; 8: 83-93
33. Agnoli A, Ruggieri S, Cerone GG, et al. The dopamine hypothesis of depression: results of treatment with dopaminergic drugs. In: Grattini S, editor. Depressive disorders. Stuttgart: FK Schatauer Verlag, 1977: 447-58
34. Bottiglieri T, Laundy M, Martin R, et al. S-adenosylmethionine influences monoamine metabolism [letter]. Lancet 1984; 2: 224
35. Bottiglieri T, Camey MWP, Edeh J, et al. A biochemical study of depressed patients receiving S-adenosylmethionine (SAM). In: Borchardt C, Ueland PM, editors. Biological methylation and drug design: experimental and clinical roles of SAM. Clifton: Humana Press Inc., 1986: 327-38
36. Yamamura HI, Enna SJ, editors. Neurotransmitter receptors: part 2. Biogenic amines. London and New York: Chapman, 1981
37. Sherer MA, Cantoni GL, Golden RN, et al. Effects of S-adenosyl-methionine on plasma norepinephrine, blood pressure, and heart rate in healthy volunteers. Psychiatry Res 1986; 17: 111-8
38. Agnoli A, Martucci N, Manna V. On the the antidepressant effect of SAMe: clinical and pharmaco-EEG study with SAMe alone and in association with a beta-2 stimulant drug, phenoterole. Clin Neuropharm 7: 104-5, 1984
39. Cohen B, Stramentinoli G, Sosa AL, et al. Effects of the novel antidepressant S-adenosylmethionine on $\alpha_1$- and $\beta$-adrenoreceptors in rat brain. Eur J Pharmacol 1989; 170: 201-7
40. Cimino M, Vantini G, Algeri S. Age-related modification of dopaminergic and beta-adrenergic receptor system: restoration to normal activity by modifying membrane fluidity with S-adenosylmethionine. Life Sci 1984; 34: 2029-39
41. Hirata F, Strittmatter WJ, Axelrod J. $\beta$-adrenergic receptor agonists increase phospholipid methylation, membrane fluidity and $\beta$-adrenergic receptor-adenylate cyclase coupling. Proc Natl Acad Sci 1979; 76: 368-72
42. Di Perri B, Calderini G, Battistella A. Phospholipid methylation increases [$^3$H]diazepam and [$^3$H]GABA binding in membrane preparations from rat cerebellum. J Neurochem 1983; 41: 302-8
43. Muccioli G, Scordamaglia A, Bertacco S, et al. Effect of S-adenosyl-L-methionine on brain muscarinic receptors of aged rats. Eur J Pharmacol 1992; 227: 293-9
44. Muccioli G, DiCarlo R. S-adenosylmethionine restores prolactin receptors in the aged rabbit brain. Eur J Pharmacol 1989; 166: 223-30
45. Wurtman RJ, Rose S, Matthyse S. L-dihydroxyphenylalanine effect on S-adenosylmethionine in brain. Science 1970; 169: 395-7
46. Surtees R, Hyland K. L-3,4-dihydroxyphenylalanine (levodopa) lowers central nervous system S-adenosylmethionine concentrations in humans. J Neurol Neurosur Psychiatry 1990 53: 569-72
47. Keating JN, Trimble KC, Mulcahy et al. Evidence of brain methyltransferase inhibition and early brain involvement in HIV positive patients. Lancet 1991; 337: 935-9
48. Surtees R, Hyland K, Smith I. Central-nervous-system methyl group metabolism in children with neurological complications of HIV infection. Lancet 1990; 335: 619-21
49. Hyland K, Surtees RAH, Rodeck C, et al. Aromatic L-amino acid decarboxylase deficiency: clinical features, diagnosis, and treatment of a new inborn error of neurotransmitter amine synthesis. Neurol 1992; 42: 1980-8
50. Pall HS, Surtees R, Sturman SG, et al. S-adenosylmethionine in cerebrospinal fluid in Parkinson's disease (PD) [abstract]. Neurology 1992; 42: 283
51. Mayeux R. Depression in the patient with Parkinson's disease. J Clin Psychiatry 1990; 51: 20-3
52. Meltzer H. Serotonergic function in depression. Br J Psychiatry 1989; 155: 25-31
53. Siever LJ, Khan RS, Lawlor BA, et al. Critical issues in defining the role of serotonin in psychiatric disorders. Am Soc Pharmacol Exp Ther 1991; 43: 509-25
54. Jellinger K. Overview of morphological changes in Parkinson's disease. In: Yahr MD, Bergmann KJ, editors. Advances in neurology: Parkinson's disease. New York: Raven Press, 1986: 1-19
55. Ruberg M, Agid Y. Dementia in Parkinson's disease. In: Iverson L, Iverson SD, Synder SH, editors. Handbook of psychopharmacology, Vol. 20. Psychopharmacology of the aging nervous system. New York: Plenum Press, 1988: 157-206

56. Mayeux R. The serotonin hypothesis of depression in Parkinson's disease. J Clin Psychiatry 1990; 53: 163-6
57. Mindham RHS, Marsden CD, Parkes JD. Psychiatric symptoms during L-dopa therapy of Parkinson's disease and their relationship to physical disability. Psychol Med 1976; 6: 23-33
58. Barbeau A. L-dopa therapy of Parkinson's disease: a critical review of nine years experience. Can Med Assoc J 1969; 101: 791-800
59. Maruyama W, Naoi M, Takahashi A, et al. The mechanism of perturbation in monoamine metabolism by L-dopa therapy: in vivo and in vitro studies. J Neural Transm Gen Sect 1992; 90: 183-97
60. Carrieri PB, Indaco A, Gentile S, et al. S-adenosylmethionine treatment of depression in patients with Parkinson's disease: a double blind, crossover study versus placebo. Curr Ther Res 1990; 48: 154-60
61. Crellin R, Bottiglieri T, Reynolds EH. Folates and Psychiatric Disorders. Drugs 1993; 45: 623-36
62. Bell IR, Edman JS, Marby DW, et al. Vitamin B12 and folate status in acute geropsychiatric inpatients: affective and cognitive characteristics of a vitamin non-deficient population. Biol Psychiatry 1990; 27: 125-37
63. Ikeda T, Furukawa Y, Mashimoto S, et al. Vitamin B12 levels in serum and cerebrospinal fluid of people with Alzheimer's dementia. Acta Psychiatr Scand 1990; 82: 327-9
64. Nijst TQ, Weavers RA, Schoonderwaldt HC, et al. Vitamin B12 and folate concentrations in serum and cerebrospinal fluid of neurological and psychiatric patients with special reference to multiple sclerosis and dementia. J Neurol Neurosurg Psychiatry 1990; 53: 951-4
65. Bottiglieri T, Godfrey P, Flynn T, et al. Cerebrospinal fluid S-adenosylmethionine in depression and dementia: effects of treatment with parenteral and oral S-adenosylmethionine. J Neurol Neurosurg Psychiatry 53: 1990; 1096-8
66. Reynolds EH, Godfrey P, Bottiglieri T, et al. S-adenosylmethionine and Alzheimer's disease [abstract]. Neurol 1989; 39 Suppl. 1: 397
67. Reynolds EH, Camey MWP, Toone BK, et al. Transmethylation and neuropsychiatry. In: Mato J, editor. Biochemical, pharmacological and clinical aspects of transmethylation. Cell Biology Reviews 1987; 2: 93-102
68. Cohen BM, Satlin A, Zubenko GS. S-adenosylmethionine in the treatment of Alzheimer's dementia. J Clin Psychopharmacol 1988; 8: 43-7
69. Williams RS, Matthysse S. Age-related changes in Down syndrome brain and the cellular pathology of Alzheimer's disease. Prog Brain Res 1986; 70: 49-67
70. Gericke GS, Hesseling PB, Brink S, et al. Leucocyte ultrastructure and folate metabolism in Down's syndrome. S Afr Med J 1977; 51: 369-74
71. Hewwitt KE, Carter G, Jancar J. Ageing in Down's syndrome. Br J Psychiatry 1985; 147: 58-62
72. Lejeune J, Rethore MO, de Blois MC, et al. Metabolism of monocarbons and trisomy 21: sensitivity to methotrexate. Ann Genet 1986; 29: 16-19
73. Chadefaux B, Rethore MO, Raoul O, et al. Cystathionine beta synthetase: gene dosage effect in trisomy 21. Biochem Biophys Res Commun 1985; 128: 40-4
74. Chadefaux B, Ceballos I, Hamet M, et al. Is absence of atheroma in Down's syndrome due to decreased homocysteine levels? [letter]. Lancet 1988; 2: 741
75. Reynolds EH. Interictal psychiatric disorders. In: Smith D, Treiman D, Trimble MR, editors. Advances in neurology. New York: Raven Press, 1991: 44-58
76. Reynolds EH. Effects of folic acid on the mental state and fit frequency of drug treated epileptic patients. Lancet 1967; 1: 1086-8
77. Trimble MR, Corbett JA, Donaldson D. Folic acid and mental symptoms in children with epilepsy. J Neurol Neurosurg Psychiatry 1980; 43: 103-4
78. Robertson MM, Trimble MR. Depressive illness in patients with epilepsia: a review. Epilepsia 1983; 24: 109-16
79. Rodin E, Schmaltz S. Folate levels in epileptic patients. In: Parsonage M, Grant RHE, Craig AG, Ward AA, editors. Advances in epileptology: XIVth Epilepsy International Symposium. New York: Raven Press, 1983; 143-53
80. Edeh J, Toone BK. Antiepileptic therapy, folate deficiency and psychiatric morbidity: a general practice survey. Epilepsia 1985; 26: 434-40
81. Reynolds EH. Anticonvulsants, folic acid and epilepsy. Lancet 1973; 1: 1376-8
82. Hommes OR, Hollinger JL, Jansen NJT, et al. Convulsant properties in folate compounds: some considerations and speculations. In: Botez MI, Reynolds EH, editors. Folic acid in neurology, psychiatry and internal medicine. New York: Raven Press, 1979: 285-316
83. Kaijima M, Riche D, Rousseva S, et al. Electroencehalographioc, behavioural and histopathological features of seizures induced by intra-amygdala application of folic acidincats. Exp Neurol 1984; 86: 313-21
84. Reynolds EH, Bottiglieri T, Laundy M, et al. Vitamin B12 metabolism in multiple sclerosis. Arch Neurol 1992; 42: 649-52
85. Crellin RF, Bottiglieri T, Reynolds EH. Multiple sclerosis and macrocytosis. Acta Neurol Scand 1991; 81: 388-91
86. Najim al-Din AS, Khojali M, Habbosh H, et al. Marcocytosis in multiple sclerosis: a study of 82 de novo Arab patients. J Neurol Neurosurg Psychiatry 1991; 54: 415-6
87. Chanarin I. The megaloblastic anaemias. 2nd ed. Oxford: Blackwell Medical Publishers, 1979; 187-97
88. Reynolds EH. Multiple sclerosis and vitamin B12 metabolism. J Neuroimmunol 992; 40: 225-30
89. Pincus JH. Folic acid deficiency: a cause of subacute combined system degeneration. In: Botez MI, Reynolds EH, editors. Folic acid in neurology, psychiatry and internal medicine. New York: Raven Press, 1979; 427-33
90. Lever EG, Elwes RDC, Williams A, Reynolds EH. Subacute combined degeneration of the cord due to folate deficiency: response to methyl folate treatment. J Neurol Neurosurg Psychiatry 1985; 49: 1203-7
91. Grandy G, Jacobson W, Sidman R. Inhibition of a transmethylation reaction in the central nervous system – an experimental model for subacute combined degeneration of the cord. J Physiology 1973; 233: IP-3P
92. Jacobson W, Gandy G, Sidman RL. Experimental subacute combined degeneration of the cord in mice. J Pathol 1973; 109 Suppl.: P13-14
93. Lee CC, Surtees R, Duchen LW. Distal motor axonopathy and central nervous system myelin vacuolation caused by cycloleucine, an inhibitor of methionine adenosyltransferase. Brain 1992; 115: 935-55
94. Scott JM, Winn J, Wilson P, et al. Pathogenesis of subacute combined degeneration: a result of methyl group deficiency. Lancet 1981; 2: 334-7
95. van der Westhuyzen J, Fernandes-Costa F, Metz J. Cobalamin inactivation by nitrous oxide produces severe neurological impairment in fruit bats: protection by methionine and aggravation by folates. Life Sci 1982; 31: 2001-10

96. Molloy AM, Weir DF, Kennedy G, et al. A new high performance liquid chromatographic method for the simultaneous measurement of S-adenosylmethionine and S-adenosylhomocysteine. Biomed Chromatogr 1990; 4: 257-60
97. Viera-Makings E, Metz J, van der Westhuyzen J, et al. Cobalamin neuropathy: is S-adenosylhomocysteine toxicity a factor? Biochem J 1990; 266: 707-11
98. Bottiglieri T, Godfery P, Carney MWP, et al. CSF S-adenosylmethionine in neurological and psychiatric patients: effects of treatment with parenteral and oral S-adenosylmethionine. In: Linnell JC, Bhatt HR, editors. Biomedicine and physiology of vitamin B12. London: Children's Medical Charity, 1990: 167-74
99. Bleyer CM. Neurological sequelae of methotrexate and ionizing radiation: a new classification. Cancer Treat Rep 1981; 65 Suppl. 1: 89-98
100. Price RA. Therapy related central nervous system diseases in children with acute lymphocytic leukaemia. In Mastrangelo R, Poplack DG, editors. Central nervous system leukaemia. Boston: Martinus Nijhoff, 1983: 71-81
101. Kamen BA, Winick N, Lester C, et al. Effect of chronic methotrexate (MTX) treatment on tissue levels of folate and MTX polymutamates (MTXGLUn). Proc Am Assoc Cancer Res 1985; 26: 232
102. Svardal AM, Ueland PM, Berge RK, et al. Effect of methotrexate on homocysteine and other sulfur compounds in tissues of rats fed a normal or a defined, choline-deficient diet. Cancer Chemother Pharmacol 1988; 21: 313-18
103. Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. Ann Neurol 1986; 19: 517-24
104. Price RW, Brew BJ. The AIDS dementia complex. J Infect Dis 1988; 158: 1079-83
105. Navia BA, Cho E-W, Petito Ck, et al. The AIDS dementia complex: II. Neuropathology Ann Neurol 1986; 19: 525-35
106. Price RW, Brew BJ, Sidtis J, et al. The brain in AIDS: central nervous system HIV-1 infection and AIDS dementia complex. Science 1988; 239: 586-92
107. Rosenblum MK. Infection of the central nervous system by the human immunodeficiency virus type 1: morphology and relation to syndromes of progressive encephalopathy and myelopathy in patients with AIDS. Pathol Annu 1990; 25 (Pt 1): 117-69
108. Petito CK, Navia BA, Cho E-S, et al. Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with the aquired immunodeficiency syndrome. New Engl J Med 1985; 312: 874-9
109. Gray F, Gheradi R, Scaravilli F. The neuropathology of the aquired immune deficiency syndrome (AIDS): a review. Brain 1988; 111: 245-66
110. McArthur JC. Neurologic manifestations of AIDS. Medicine 1987; 66: 408-37
111. Lemann W, Cho E-S, Melsen S, Petito C. Neuropathological findings in 104 cases of aquired immune deficiency syndrome (AIDS): an autopsy study. J Neuropath Exp Neurol 1985; 44: 349A
112. Lantos PL, McLaughlin JE, Scholtz CL, et al. Neuropathology of the brain in HIV infection. Lancet 1989; 1: 309-11
113. Bottiglieri T. Methylation and neurological complications of HIV infection: the effect of intravenous SAMe administration in restoring CNS methyl group metabolism. Ann Psiquiatr 1992; 8 Suppl. 1: 22-3
114. Allegra CJ, Chabner BA, Tuazon CU, et al. Trimetrexate for the treatment of *Pneumocystis carinii* pneumonia in patients with the aquired immune deficiency syndrome. N Engl J Med 1987; 317: 978-85
115. Gordin FM, Simon GL, Wofsy CB, et al. Adverse reactions to trimethoprim-sulmethoxazole in patients with the aquired immunodeficiency syndrome. Ann Int Med 1984; 100: 495-9

Correspondence and reprints: Dr *T. Bottiglieri,* Metabolic Disease Center, Baylor Research Institute, 3812 Elm Street, Dallas, TX 75226, USA.