

Hypothesis on the pathogenesis of vacuolar myelopathy, dementia, and peripheral neuropathy in AIDS

S V Tan, R J Guilloff

Abstract

Certain aspects of the clinical syndrome of dementia, cerebral atrophy, predominantly sensory neuropathy, and vacuolar myelopathy in AIDS resemble those seen in vitamin B12 deficiency. Pathologically, there are similarities not only in the changes in the spinal cord, but also in the brain and peripheral nerves. The pathogenesis of vacuolar myelopathy may be secondary to a combination of immune mediated myelin and oligodendrocyte injury, and simultaneous impairment of repair mechanisms due to a deficiency of S-adenosylmethionine (SAM). Products derived from macrophages may interfere directly with the methyl transfer cycle through the generation of reactive oxygen intermediates and reactions involving nitric oxide and peroxynitrite which may limit the supply of methionine for conversion to SAM, both by direct interaction as well as through inhibition of methionine synthase. Macrophage activation with secretion of cytokines and other biologically reactive substances within the nervous system is sustained in the late stages of HIV infection by the general effects of immune depletion, including loss of T cells (with concomitant reduction of macrophage regulatory molecules) and recurrent opportunistic infections, and may be further augmented by the local presence of the virus itself (or its surface glycoprotein gp120). This would account for the common, but not exclusive, occurrence of vacuolar myelopathy in AIDS. The ability of the virus and its products to stimulate macrophage and microglial activation may also explain the association between severity of vacuolar myelopathy and the presence of HIV encephalitis. A similar mechanism may underlie the pathogenesis of dementia, cerebral atrophy, and peripheral neuropathy. Local factors or differential susceptibility between the central and peripheral nervous system may determine whether myelinotoxic or neurotoxic processes predominate; the prominence of myelin involvement in the spinal cord, and axonal involvement peripherally may reflect both ends of this range, with the brain manifesting a more equal balance of both processes.

(*J Neurol Neurosurg Psychiatry* 1998;65:23-28)

Keywords: AIDS; myelopathy; peripheral neuropathy; dementia

Publications support an indirect relation between HIV and the pathogenesis of vacuolar myelopathy, peripheral neuropathy, and dementia. The role of products and cytokines derived from macrophages or microglia has been emphasised by some,¹⁻⁴ and defective methylation due to a deficiency of S-adenosylmethionine (SAM) by others,⁵⁻⁸ with some suggesting that the two may be linked.⁵

We propose that concomitant SAM depletion and cytokine or oxygen mediated toxicity underlie myelin and neuronal damage in AIDS. The SAM depletion may occur as a result of (a) reduced SAM production secondary to limitation in methionine availability due to reduced methionine production caused by inhibition of methionine synthase by macrophage derived nitric oxide (NO), and oxidation of methionine by peroxynitrite, and (b) increased consumption of SAM in repair mechanisms triggered by the toxic effects of cytokines and oxygen radicals on myelin or membranes.

This model suggests a direct link between macrophage activation and SAM depletion in AIDS and explains the neuroanatomical lesions in vacuolar myelopathy, which is pathologically indistinguishable from subacute combined degeneration of the cord (SACD).^{9,10} A similar clinicopathological syndrome of dementia, vacuolar myelopathy, peripheral neuropathy, and SAM depletion is seen in vitamin B12 deficiency.

The proposed pathogenesis is discussed in the following order: vacuolar myelopathy, dementia, and peripheral neuropathy. Figure 1 shows a summary of the pathogenetic cascade. Figure 2 shows the relation of methionine, vitamin B12, and folate with SAM production and the association of the single carbon transfer pathway with glutathione metabolism.

Vacuolar myelopathy

(A) ACTIVATION OF MACROPHAGES, MONOCYTES, OR MICROGLIA

The secretion of immunoactive or toxic substances by activated macrophages and microglia contributes to CNS immunopathology in AIDS.^{1,2,11} Factors which may contribute to macrophage activation within the CNS in AIDS (figure 1) include: (a) decreased production of macrophage regulatory lymphokines interleukin-4 (IL-4) and IL-10²; (b) recurrent infections; (c) increasing viral load and interaction of gp120 with macrophages leading to cytokine interleukin 1 (IL-1) and arachidonic acid metabolite production¹²; (d)

Neuromuscular Unit,
West London Centre
and University
Department of Clinical
Neurosciences,
Charing Cross
Hospital, London, UK
S V Tan
R J Guilloff

Correspondence to:
Dr R J Guilloff,
Neuromuscular Unit (1st
Floor Pilot Wing), Charing
Cross Hospital, Fulham
Palace Road, London W6
8RF, UK. Telephone 0044
181 746 8319; fax 0044 181
746 8420; email
r.guiloff@cxwms.ac.uk

Received 11 July 1997 and in
final revised form 20 January
1998
Accepted 20 January 1998

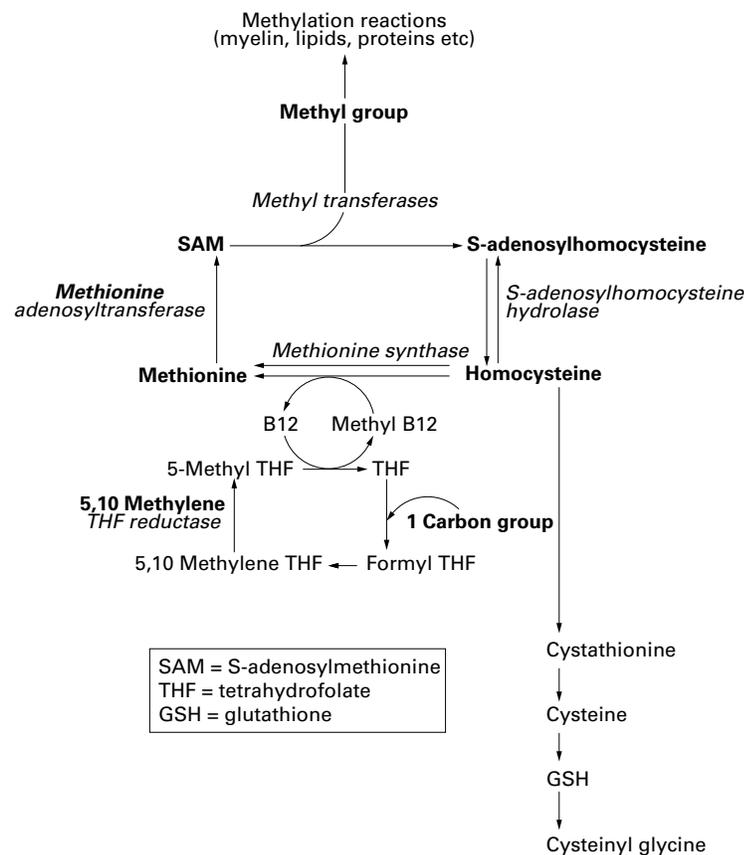


Figure 2 The single carbon (methyl) transfer pathway. Relation with B12 and glutathione metabolism. (Modified from Surtees 1993, Bottiglieri et al 1994, and Castagna et al 1995.^{7,8,10})

and methionine residues on proteins and peptides.³⁵ Also, peroxynitrous acid produces the highly reactive hydroxyl free radical (fig 1).^{35,36} Such oxidative damage to the membranes of oligodendrocytes will result in an increased demand for SAM for repair (see later) and increased consumption of antioxidants such as glutathione (GSH, fig 2).

Other factors capable of mediating oligodendrocyte injury include TNF β produced by activated lymphocytes, and antibody dependent cell mediated cytotoxicity. TNF β causes oligodendrocyte apoptosis.³⁷ The production of intrathecal antibody³⁸ to HIV raises the possibility that natural killer cells bearing antibodies to gp120 may attack oligodendrocytes with myelin associated glycoprotein-bound gp120 on their surface. As vacuolar myelopathy is not associated with significant inflammatory infiltrates, TNF β and lymphocyte cytotoxicity are likely to play only subsidiary roles in its pathogenesis.

(C) S-ADENOSYLMETHIONINE (SAM) DEPLETION

The mechanisms for SAM depletion and the links with the products of activated macrophages and microglia in HIV disease will be outlined. A possible explanation for the observations made on the concentrations of various components of the methyl transfer cycle in these patients, some of whom had myelopathy^{5,6,8} will also be suggested.

SAM is the mammalian "universal" methyl group donor in the brain, and is responsible for

the biological methylations that modify proteins (including myelin basic protein), nucleic acids, fatty acids, porphyrins, phospholipids, polysaccharides, and biogenic amines such as catecholamines.^{10,39} A SAM deficiency is critical to the development of demyelination in cobalamin (vitamin B12) deficiency.^{10,40} It may also be essential to the pathogenesis of vacuolar myelopathy.⁵

Comparisons of CSF concentrations of the components of the methyl transfer pathway in HIV seropositive patients with neurological disease and HIV seronegative controls show decreased SAM,^{5,6,8} increased S-adenosylhomocysteine (SAH) and reduced SAM/SAH (methylation) ratio,⁶ normal homocysteine,⁸ and normal or occasionally low methionine (fig 2).⁵ Decreased concentrations of folate in CSF were found by some authors⁵ but not by others.⁸ Studies of the components of the trans-sulphuration pathway, showed decreased concentrations of glutathione and cysteinyl glycine but normal concentrations of cysteine in CSF (fig 2).⁸

The low concentrations of SAM in patients with HIV with neurological disease may be caused by excessive consumption of SAM in methylation reactions for repair of immunological damage to the CNS.⁵ The reasons for the apparent inability of the methyl transfer cycle to generate sufficient SAM are unknown. The linear relation between SAM and methionine concentrations in CSF in patients with HIV but not in controls suggests that the availability of methionine may be limiting the production of SAM.⁵ The reasons for limitation of methionine availability are unclear. A deficiency of 5-methyltetrahydrofolate induced by macrophage secreted neopterin has been suggested,⁵ but there is no evidence of folate deficiency in patients with HIV with neurological complications (including myelopathy).⁸

The supply of methionine is determined by the activity of the vitamin B12 dependent methionine synthase, acting on homocysteine (fig 2). The diet⁴¹ is unlikely to be an adequate source, as the neurological consequences of SAM deficiency occur when methionine synthase is inhibited by B12 or folate deficiency or nitrous oxide misuse.^{42,43}

Vitamin B12 deficiency may exacerbate SAM deficiency in some patients, but it cannot be the primary cause. Firstly, most patients with vacuolar myelopathy do not have B12 deficiency.^{9,18} Secondly, although B12 deficiency is common in AIDS,⁴⁴ those shown to be SAM deficient were B12 and folate replete.^{6,8}

Limitation in the bioavailability of methionine may relate to the production of NO and peroxynitrite by activated macrophages and microglia. Peroxynitrite oxidises methionine to ethylene or methionine sulphoxide.³⁴ This powerful oxidant may be generated in the vicinity of activated macrophages which are capable of secreting NO and superoxide simultaneously, and is likely to cause local reduction in methionine concentrations.

Bovine heart cytochrome c oxidase catalyses the reduction of NO to nitrous oxide in

anaerobic conditions,⁴⁵ raising the further possibility that NO derived from macrophages gives rise to nitrous oxide *in vivo* with consequent methionine synthase inhibition and neurological sequelae—such as SACD—as seen in nitrous oxide misuse.^{42–43} Also, NO itself may cause a rapid dose dependent inhibition of methionine synthase.⁴⁶ Reduced CNS concentrations of glutathione in patients with HIV may further contribute to impairment of methionine synthase activity.^{8, 47}

Methionine synthase inhibition in isolation normally causes a rise in homocysteine concentrations, but this was not found.⁸ Homocysteine concentrations may be kept within normal limits by several mechanisms. Firstly, with the production of oxygen radicals by macrophages in AIDS, homocysteine may be consumed by the trans-sulphuration pathway to replenish falling concentrations of the antioxidant glutathione, which was found to be low in these patients (fig 2).⁸ Secondly, the kinetics of the enzyme SAH hydrolase (fig 2) favour the formation of SAH, the reaction *in vivo* being normally driven in the opposite direction (of homocysteine) only by the rapid removal of homocysteine and adenine.¹⁰ Normal or rising homocysteine concentrations would therefore be expected to favour the conversion of homocysteine to SAH. This may also account for the high concentrations of SAH and low methylation ratio.⁶

Thus, in AIDS, macrophage derived products in the CNS may lead to increased consumption of SAM, and simultaneously limit its production. Where SAM deficiency is sustained chronically, this may lead to the clinical and pathological changes of vacuolar myelopathy. Such a link between macrophage activation and SAM metabolism may account for the high incidence of vacuolar myelopathy in AIDS, as well as its occurrence in immunosuppressed HIV seronegative people.⁴⁸

Dementia and cerebral atrophy

The brains of patients with AIDS with dementia or cerebral atrophy show varying degrees of demyelination, neuronal loss, gliosis, microglial activation, multinucleated giant cells, and detectable HIV antigen or RNA.^{49–50} Probable mechanisms responsible for the non-specific neuropathological changes are as follows: (a) the gliosis results from astrocyte proliferation in response to TNF α ⁵¹; (b) the myelin pallor may be due to SAM deficiency or the production of TNF α or other cytokines and oxygen radicals^{11, 52}; and (c) the neuronal loss⁵³ may be due to local production of neurotoxins such as quinolinic acid,⁵⁴ arachidonic acid metabolites,²⁰ free radicals, and NO.²⁸ NO, produced by certain types of neurons³⁶ as well as macrophages, microglia, and astrocytes, may also mediate the neurotoxicity of gp120.⁵⁵

The presence and degree of dementia and/or cerebral atrophy cannot be correlated specifically with any one neuropathological feature.^{3, 50} Several explanations could be forwarded.

Firstly, the neurological features may be the product of variably contributing factors, in

each person (fig 1). Gliosis, myelin pallor, or neuronal loss may be more prominent in some patients, whereas in others multinucleated giant cells and microglial nodules may predominate if the level of productive viral infection is high. The degree of SAM deficiency may contribute to the extent of demyelination. In B12 deficiency, demyelination may vary from small, often perivascular, foci to dissemination over wide areas of the corona radiata, sometimes accompanied by diffuse gliosis,⁵⁶ closely resembling descriptions in AIDS.⁵⁷

Secondly, impairment of neurotransmitter function (as in SAM deficiency), which may contribute to AIDS dementia, is not detectable by routine histopathological techniques. The SAM dependent enzymatic methylation of phospholipids plays an important part in the transduction of receptor mediated signals through cellular membranes. Catecholamine neurotransmitters interacting with cell surface receptors initiate a cascade of biochemical and physical changes in local domains of the membrane leading to increased phospholipid methylation and mobility of receptors.⁵⁸ Concentrations of SAM in the CSF also seem to influence brain monoamine metabolism.⁵⁹

Peripheral neuropathy

A distal symmetric predominantly sensory axonal neuropathy (DSPN) of unknown aetiology is common in AIDS. Some authors distinguish between the painful and non-painful subgroups,⁶⁰ whereas others do not.⁶¹ In HIV disease, as in HIV seronegative people, both painful and non-painful distal neuropathies are heterogeneous entities. A proportion of the painful subgroup may be caused by cytomegalovirus (CMV)^{60, 62, 63}; other causes include vasculitis,⁶⁴ drugs,⁶⁵ inflammatory processes,⁶⁶ nutritional deficiencies, and diabetes. However, in most patients with DSPN, no cause is found. Macrophage mediated immunopathology, together with SAM depletion, may be important factors in the pathophysiology of DSPN in AIDS. The mechanism of macrophage recruitment in peripheral neuropathy may be similar to that described for vacuolar myelopathy.

Vitamin B12 deficiency may present as a painful, or non-painful neuropathy.^{67, 68} There is no correlation between serum B12 concentrations and the presence of distal sensory peripheral neuropathy in AIDS.⁶⁹ As described in vacuolar myelopathy, SAM deficiency can occur with normal serum concentrations of B12 and folate and may contribute to the pathophysiology of DSPN.

Wallerian-like degeneration of myelinated and unmyelinated fibres, and distal axonal degeneration involving both the peripheral and central branches occur in DSPN.^{60, 61, 70} Axonal atrophy seems to be found in painful but not in non-painful peripheral neuropathy.⁷⁰ The pathology of peripheral neuropathy in B12 deficiency is poorly documented but a similar reduction in numbers of myelin sheaths and axons, with degeneration in the centrally directed posterior root fibres, has been

described.⁷¹ In B12 deficiency in monkeys, both Wallerian type axonal and myelin degeneration were seen in the peripheral nerves.⁷²

Macrophages expressing TNF α within degenerating nerve fibres seem to be activated to a greater extent, and present in higher density for a given degree of Wallerian-like degeneration in AIDS, compared with seronegative controls with neuropathy.⁶¹ Cytokines secreted by activated macrophages may account for the damage to unmyelinated and myelinated fibres.

Clinical implications

Supplementation with SAM has been used clinically in the treatment of various disorders including depression⁷ and osteoarthritis.⁷³ Concentrations of SAM in the CSF can be raised by systemic oral SAM supplementation.^{8, 40} By contrast with methionine, it seems to be relatively non-toxic, both in short and long term animal studies and in over 10 years of clinical use.⁷⁴ Also, there has been recent *in vitro* evidence that SAM may protect transplanted hepatocytes from the toxic effects of cytokines,⁷⁵ prevent glutamate cytotoxicity in cultured cortical neurons,⁷⁶ and raise glutathione concentrations in CSF.⁸ If this hypothesis is correct, SAM supplementation early in HIV disease may significantly reduce the incidence of vacuolar myelopathy, dementia, and peripheral neuropathy.

- Tyor WR, Glass JD, Baumrind N, *et al.* Cytokine expression of macrophages in HIV-1-associated vacuolar myelopathy. *Neurology* 1993;43:1002-9.
- Wesselingh SL, Glass J, McArthur JC, *et al.* Cytokine dysregulation in HIV-associated neurological disease. *Adv Neuroimmunol* 1994;4:199-206.
- Tyor WR, Wesselingh SL, Griffin JL, *et al.* Unifying hypothesis for the pathogenesis of HIV-associated dementia complex, vacuolar myelopathy, and sensory neuropathy. *J Acquir Immune Defic Syndr Hum Retroviro* 1995;9:379-88.
- Tan SV, Guilloff RJ, Henderson DC, *et al.* AIDS-associated vacuolar myelopathy and tumor necrosis factor- α . *J Neurol Sci* 1996;138:134-44.
- 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.
- Keating JN, Trimble KC, Mulcahy F, *et al.* Evidence of brain methyltransferase inhibition and early brain involvement in HIV-positive patients. *Lancet* 1991;337:935-9.
- Bottiglieri T, Hyland K, Reynolds EH. The clinical potential of ademetionine (S-adenosylmethionine) in neurological disorders. *Drugs* 1994;48:137-52.
- Castagna A, Le Grazie C, Accordini A, *et al.* Cerebrospinal fluid S-adenosylmethionine (SAMe) and glutathione concentrations in HIV infection: effect of parenteral treatment with SAMe. *Neurology* 1995;45:1678-83.
- Petito CK, Navia BA, Cho ES, *et al.* Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1985;312:874-9.
- Surtees R. Biochemical pathogenesis of subacute combined degeneration of the spinal cord and brain. *J Inherit Metab Dis* 1993;16:762-70.
- Tyor WR, Glass JD, Griffin JW, *et al.* Cytokine expression in the brain during the acquired immunodeficiency syndrome. *Ann Neurol* 1992;31:349-60.
- Wahl LM, Corcoran ML, Pyle SW, *et al.* Human immunodeficiency virus glycoprotein (gp120) induction of monocyte arachidonic acid metabolites and interleukin 1. *Proc Natl Acad Sci (USA)* 1989;86:621-5.
- Benveniste EN. Cytokine circuits in the brain: implications for AIDS dementia complex. In: Price RW, Perry SW, eds. *HIV, AIDS and the brain*. New York: Raven Press, 1994;72: 71-88.
- Poli G, Kinter A, Justement JS, *et al.* Tumor necrosis factor α functions in an autocrine manner in the induction of human immunodeficiency virus expression. *Proc Natl Acad Sci (USA)* 1990;87:782-5.
- Rosenberg ZF, Fauci AS. Cytokine induction of HIV expression. *Immunol Today* 1990;11:176-80.
- Weiser B, Peress N, La Neve D, *et al.* Human immunodeficiency virus type 1 expression in the central nervous system correlates directly with extent of disease. *Proc Natl Acad Sci USA* 1990;87:3997-4001.
- Rosenblum M, Scheck AC, Cronin K, *et al.* Dissociation of AIDS-related vacuolar myelopathy and productive HIV-1 infection of the spinal cord. *Neurology* 1989;39:892-6.
- Tan SV, Guilloff RJ, Scaravilli F. AIDS-associated vacuolar myelopathy - a morphometric study. *Brain* 1995;118:1247-61.
- Petito CK, Vecchio D, Chen Y-T. HIV antigen and DNA in AIDS spinal cords correlate with macrophage infiltration but not with vacuolar myelopathy. *J Neuropathol Exp Neurol* 1994;53:86-94.
- Genis P, Jett M, Bernton EW, *et al.* Cytokines and arachidonic metabolites produced during human immunodeficiency virus (HIV)-infected macrophage-astroglia interactions: implications for the neuropathogenesis of HIV disease. *J Exp Med* 1992;176:1703-18.
- Twerdy DJ, Glazer EW, Mott PL, *et al.* Modulation by tumor necrosis factor- α of human astroglial cell production of granulocyte-macrophage colony-stimulation factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF). *J Neuroimmunol* 1991;32:269-78.
- Rosenberg ZF, Fauci AS. Immunopathogenesis of HIV infection. *FASEB J* 1991;5:2382-90.
- Selmaj KW, Raine CS. Tumor necrosis factor mediates myelin and oligodendrocyte damage *in vitro*. *Ann Neurol* 1988;23:339-46.
- Apostolski S, McAlarney T, Quattrini A, *et al.* The gp120 glycoprotein of human immunodeficiency virus type 1 binds to sensory ganglion neurons. *Ann Neurol* 1993;34: 855-63.
- van den Berg LH, Sadiq SA, Lederman S, *et al.* The gp120 glycoprotein of HIV-1 binds to sulfatide and to the myelin associated glycoprotein. *J Neurosci Res* 1992;33:513-8.
- Sherry B, Cerami A. Cachectin/tumor necrosis factor exerts endocrine, paracrine, and autocrine control of inflammatory responses. *J Cell Biol* 1988;107:1269-77.
- Goudreau G, Carpenter S, Beaulieu N, *et al.* Vacuolar myelopathy in transgenic mice expressing human immunodeficiency virus type 1 proteins under the regulation of the myelin basic protein promoter. *Nat Med* 1996;2:655-61.
- Bukrinsky MI, Nottet HSLM, Schmidtmayerova H, *et al.* Regulation of nitric oxide synthase activity in human immunodeficiency virus type 1 (HIV-1)-infected monocytes: implications for HIV-associated neurological disease. *J Exp Med* 1995;181:735-45.
- Stuehr DJ, Cho HJ, Kwon NS, *et al.* Purification and characterization of the cytokine-induced macrophage nitric oxide synthase: an FAD- and FMN-containing flavoprotein. *Proc Natl Acad Sci (USA)* 1991;88:7773-7.
- McCall T, Vallence P. Nitric oxide takes centre-stage with newly defined roles. *Trends Pharmacol Sci* 1992;13:1-6.
- Miller B, Sarantis M, Traynelis SF, *et al.* Potentiation of NMDA receptor currents by arachidonic acid. *Nature* 1992;355:722-5.
- Radi R, Beckman JS, Bush KM, *et al.* Peroxynitrite-induced membrane lipid peroxidation: the cytotoxic potential of superoxide and nitric oxide. *Arch Biochem Biophys* 1991; 288:481-7.
- Radi R, Beckman JS, Bush KM, *et al.* Peroxynitrite oxidation of sulfhydryls. The cytotoxic potential of superoxide and nitric oxide. *J Biol Chem* 1991;266:4244-50.
- Pryor WA, Jin X, Squadrito GL. One- and two-electron oxidations of methionine by peroxynitrite. *Proc Natl Acad Sci (USA)* 1994;91:11173-7.
- Olanow CW. A radical hypothesis for neurodegeneration. *Trends Neurosci* 1993;16:439-44.
- Snyder SH. Nitric oxide and neurons. *Curr Opin Neurobiol* 1992;2:323-7.
- Selmaj K, Raine CS, Farooq M, *et al.* Cytokine cytotoxicity against oligodendrocytes: apoptosis induced by lymphotoxin. *J Immunol* 1991;147:1522-9.
- Chiodi F, Norkrans F, Hagberg L, *et al.* Human immunodeficiency virus infection of the brain. II Detection of intrathetically synthesized antibodies by enzyme linked immunosorbent assay and imprint immunofixation. *J Neurol Sci* 1988;87:37-48.
- Baldessarini RJ. Neuropharmacology of S-adenosyl-L-methionine. *Am J Med* 1987 83(suppl 5A):95-103.
- 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.
- Scott JM, Weir DG. The methyl folate trap. *Lancet* 1981;ii:337-40.
- Dinn JJ, McCann S, Wilson P, *et al.* Animal model for subacute combined degeneration. *Lancet*:1978;ii:1154.
- Layser RB. Myeloneuropathy after prolonged exposure to nitrous oxide. *Lancet* 1978;ii:1227-30.
- Harriman GR, Smith PD, Horne MK, *et al.* Vitamin B12 malabsorption in patients with acquired immunodeficiency syndrome. *Arch Intern Med* 1989;149:2039-41.
- Zhao XJ, Sampath J, Caughey WS. Cytochrome c oxidase catalysis of the reduction of nitric oxide to nitrous oxide. *Biochem Biophys Res Commun* 1995;212:1054-60.
- Nicolaou A, Ast T, Garcia CV, *et al.* *In vitro* NO and N₂O inhibition of the branch point enzyme vitamin B12 dependent methionine synthase from rat brain synaptosomes. *Biochem Soc Trans* 1994;22:296S.
- Pajares M, Duran C, Corrales F, *et al.* Modulation of rat liver S-adenosylmethionine synthetase activity by glutathione. *J Biol Chem* 1992;367:17598-605.
- Kamin SS, Petito CK. Idiopathic myelopathies with white matter vacuolation in non-acquired immunodeficiency syndrome patients. *Hum Pathol* 1991;22:816-24.
- Gelman BB, Guinto FC Jr. Morphometry, histopathology, and tomography of cerebral atrophy in the acquired immunodeficiency syndrome. *Ann Neurol* 1992;31:32-40.

- 50 Glass JD, Wesselingh SL, Selnes O, *et al.* Clinical-neuropathological correlations in HIV-associated dementia. *Neurology* 1993;43:2230-7.
- 51 Lachman LB, Brown DC, Dinarello CA. Growth promoting effect of recombinant interleukin-1 and tumor necrosis factor for a human astrocytoma cell line. *J Immunol* 1987;144:129-35.
- 52 Wesselingh SL, Power C, Glass JD, *et al.* Intracerebral cytokine messenger RNA expression in acquired immunodeficiency syndrome dementia. *Ann Neurol* 1993;33:576-82.
- 53 Everall IP, Luthert PJ, Lantos PL. Neuronal loss in the frontal cortex in HIV infection. *Lancet* 1991;337:1119-21.
- 54 Heyes MP, Brew BJ, Martin A, *et al.* Quinolinic acid in cerebrospinal fluid and serum in HIV-1 infection: relationship to clinical and neurological status. *Ann Neurol* 1991;29:202-9.
- 55 Dawson VL, Dawson TM, Uhl GR, *et al.* Human immunodeficiency virus type 1 coat protein neurotoxicity mediated by nitric oxide in primary cortical cultures. *Proc Natl Acad Sci (USA)* 1993;90:3256-9.
- 56 Duchen LW, Jacobs JM. Nutritional deficiencies and metabolic disorders. In: Adams JH, Duchen LW, eds. *Greenfield's neuropathology*. 5th ed. London: Edward Arnold, 1992: 811-80.
- 57 Schmidbauer M, Huemer M, Cristina S, *et al.* Morphological spectrum, distribution, and clinical correlation of white matter lesions in AIDS brains. *Neuropathol App Neurobiol* 1992;18:489-501.
- 58 Hirata F, Axelrod J. Phospholipid methylation and biological signal transmission. *Science* 1980;209:1082-90.
- 59 Bottiglieri T, Laundry M, Martin R, *et al.* S-adenosylmethionine influences monoamine metabolism. *Lancet* 1984;i:224.
- 60 Fuller GN, Jacobs JM, Guilloff RJ. Nature and incidence of peripheral nerve syndromes in HIV infection. *J Neurol Neurosurg Psychiatry* 1993;56:372-81.
- 61 Griffin JW, Wesselingh SL, Griffin DE, *et al.* Peripheral nerve disorders in HIV infection: similarities and contrasts with central nervous system disorders. In: Price RW, Perry SW, eds. *HIV, AIDS, and the brain*. New York: Raven Press, 1994;72:159-82.
- 62 Fuller GN, Jacobs JM, Guilloff RJ. Association of painful peripheral neuropathy in AIDS with cytomegalovirus infection. *Lancet* 1989;ii:937-41.
- 63 Mastroianni CM, Sebastiani G, Folgori F, *et al.* Detection of cytomegalovirus-matrix protein (pp65) in leukocytes of HIV-infected patients with painful peripheral neuropathy. *J Med Virol* 1994;44:172-5.
- 64 Chamouard JM, Smadja D, Chaunu MP, *et al.* Neuropathie par vasculite nécrosante au cours de l'infection par le VIH1 (Neuropathy caused by necrotizing vasculitis in HIV-1 infection). *Rev Neurol* 1993;149:358-61.
- 65 Simpson DM, Tagliati M. Nucleoside analogue-associated peripheral neuropathy in human immunodeficiency virus infection. *J Acquir Immune Defic Syndr Hum Retroviro* 1995;9:153-61.
- 66 Lipkin WI, Parry G, Kiproff D, *et al.* Inflammatory neuropathy in homosexual men with lymphadenopathy. *Neurology* 1985;35:1479-83.
- 67 Victor M, Lear AA. Subacute combined degeneration of the spinal cord. Current concepts of the disease process. Value of serum vitamin B12 determinations in clarifying some of the common clinical problems. *Am J Med* 1956;896-911.
- 68 Heaton EB, Savage DG, Brust JCM, *et al.* Neurologic aspects of cobalamin deficiency. *Medicine* 1991;70:229-45.
- 69 Veilleux M, Paltiel O, Falutz J. Sensorimotor neuropathy and abnormal vitamin B12 metabolism in early HIV infection. *Can J Neurol Sci* 1995;22:43-6.
- 70 Fuller GN, Jacobs JM, Guilloff RJ. Axonal atrophy in the painful peripheral neuropathy of AIDS. *Acta Neuropathol (Berl)* 1990;81:198-203.
- 71 Foster D B. Degeneration of peripheral nerves in pernicious anemia. *Archives of Neurology and Psychiatry* 1945;54:102-9.
- 72 Scott JM, Dinn J, Wilson P, *et al.* Subacute combined degeneration. *Lancet* 1982;i:51-2.
- 73 Berger R, Nowak H. A new medical approach to the treatment of osteoarthritis. Report of an open phase IV study with ademetionine. *Am J Med* 1987;83(suppl 5A):84-8.
- 74 Stramentinoli G. Pharmacologic aspects of S-adenosylmethionine. *Am J Med* 1987;83(suppl 5A):35-42.
- 75 Vara E, Arias-Diaz J, Garcia C, *et al.* S-adenosyl-methionine may protect transplanted hepatocytes against the toxic effects of cytokines. *Transplant Proc* 1994;26:3364-6.
- 76 Akaike A, Tamura Y, Sato Y, *et al.* Protective effects of a vitamin B12 analog, methylcobalamin, against glutamate cytotoxicity in cultured cortical neurons. *Eur J Pharmacol* 1993;241:1-6.