Table 1 *IL-1A and IL-1B genotype frequencies in healthy controls (HC) and in patients with multiple sclerosis (MS) as well as in patients with different disease courses (benign and non-benign)*

	MS	HC	Benign MS	Non-benign MS
<i>IL-1A</i> genotype (% (n)):				
CC	47 (189)	45 (198)	43 (39)	52 (56)
CT	45 (177)	46 (203)	43 (39)	43 (46)
TT	8 (33)	9 (38)	14 (13)	5 (5)
<i>IL-1B</i> genotype (% (n)):				
CC	38 (123)	39 (159)	34 (25)	33 (27)
CT	48 (155)	50 (201)	44 (32)	56 (46)
TT	14 (43)	11 (43)	22 (16)	11 (9)

by sex or age (data not shown). We found a similar gene free distribution between patients with multiple sclerosis and healthy controls for both *IL-1A* and *IL-1B* polymorphisms (table) (*IL-1A*: multiple sclerosis *v* healthy controls, $\chi^2=0.5$, NS; *IL-1B*: multiple sclerosis *v* healthy controls, $\chi^2=1.3$, NS).

The possible association between a given *IL-1A* or *IL-1B* genotype and accumulation of clinical burden over time was assessed by comparing two groups of patients with multiple sclerosis differing for their disease outcome and classified as "benign" (patients with a stabilised expanded disability status scale (EDSS) score ≤ 3 after at least 10 years from disease onset) and "non-benign" (patients with an EDSS score > 3 within 10 years from disease onset, table).³ In the case of the *IL-1A* polymorphism, the gene frequency of 91 benign was not statistically different from those of the 107 non-benign patients with multiple sclerosis ($\chi^2=5.9$, NS). As for the *IL-1B* polymorphism, the gene frequency of the 73 benign patients was also similar to those of the 82 non-benign patients with multiple sclerosis ($\chi^2=4.0$, NS).

To assess whether *IL-1A* and/or *IL-1B* genotypes had an influence on the age at onset of multiple sclerosis, Kaplan-Meier disease free survival curves were calculated, plotting the age at disease onset of each patient versus the respective *IL-1* genotype (data not shown). Again, neither *IL-1A* (log rank $\chi^2=3.9$, NS) nor *IL-1B* (log rank $\chi^2=0.72$, NS) genotypes seemed to affect the distribution of the age at multiple sclerosis onset.

A handful of inflammation associated polymorphisms have been shown to positively associate with the occurrence of multiple sclerosis or to influence its clinical variables, including polymorphisms located within or nearby the HLA locus (important for multiple sclerosis susceptibility), or the *IL-1RN*, *IL-4* and *IL-1B* genes¹ (possibly important in modulating the course of disease).

Our analysis could not demonstrate any association between these two previously untested *IL-1A* and *IL-1B* promoter polymorphisms and the occurrence of multiple sclerosis, the age at disease onset, or the accumulation of clinical burden over time in affected patients.

Given the inflammatory nature of multiple sclerosis pathological lesions and the positive association of the related *IL-1RN* VNTR with some of the clinical features of multiple sclerosis, these results are somewhat unexpected and contrast with data coming from similar genetic studies in Alzheimer's disease, a degenerative disease of the CNS where the role of inflammatory mechanisms is not as established as in multiple sclerosis.⁴

These data contribute to the debate over the role of inflammation in multiple sclerosis,

especially as recent reports have surprisingly suggested that inflammation may even be protective (rather than having a pathogenic role) in experimental animal models of multiple sclerosis.⁵

This work was supported by a grant from the Armenise-Harvard Foundation.

CINZIA FERRI

FRANCESCA LUISA SCIACCA

LUIGI MARIA EDOARDO GRIMALDI

Department of Neuroscience, Neuroimmunology Unit, DIBIT, Department of Neuroscience, San Raffaele Scientific Institute, via Olgettina 58, 20132 Milano, Italy

FABRIZIO VEGLIA

Institute for Scientific Interchange Foundation, Torino, Italy

GIUSEPPE MAGNANI

GIUSEPPE SANTUCCIO

GIANCARLO COMI

NICOLA CANAL

Multiple Sclerosis Center

LUIGI MARIA EDOARDO GRIMALDI

IRCCS Oasi Maria Santissima, Troina, Italy

Correspondence to: Dr L M E Grimaldi

luigi.grimaldi@hsr.it

- 1 Brosnan CF, Cannella B, Battistini L, *et al*. Cytokine localization in multiple sclerosis lesions: correlation with adhesion molecule expression and reactive nitrogen species. *Neurology* 1995;45:S16-21.
- 2 Iamamura K, Suzumura A, Hayashi F, *et al*. Cytokine production by peripheral blood monocytes/macrophages in multiple sclerosis patients. *Acta Neurol Scand* 1993;87:281-5.
- 3 Sciacca FL, Ferri C, Vandenbroeck K, *et al*. Relevance of interleukin-1 receptor antagonist intron 2 polymorphism in Italian MS patients. *Neurology* 1999;52:1896-8.
- 4 Grimaldi LME, Casadei VM, Ferri C, *et al*. Association of early onset Alzheimer's disease with an interleukin-1a gene polymorphism. *Ann Neurol* 2000;47:361-5.
- 5 Kerschensteiner M, Gallmeier E, Behrens L, *et al*. Activated human T cells, B cells, and monocytes produce brain-derived neurotrophic factor in vitro and in inflammatory brain lesions: a neuroprotective role of inflammation. *J Exp Med* 1999;189:865-70.

Hyperhomocysteinaemia in Alzheimer's disease and expression of cell cycle markers in the brain

We report that moderately increased concentrations of serum total homocysteine in Alzheimer's disease are associated with the expression of cyclin E (a marker of entry into the cell division cycle) in neurons of the hippocampus. Aberrant entry of neurons into the cell cycle might be an early step in the pathological process.

Expression of proteins related to the control of the cell division cycle has been found in the nuclei of neurons in the cerebral cortex in Alzheimer's disease and it has been proposed that the expression of such proteins, in the absence of cell division, might lead to death of neurons by apoptosis or to the development of neurofibrillary pathology.¹ If the aberrant expression of cell cycle markers is part of the pathological process, then it is important to identify possible factors that might trigger the entry of neurons into the cell cycle. Moderately increased concentrations of plasma total homocysteine, an established risk factor for vascular disease,² are also associated with histopathologically confirmed Alzheimer's disease.³ As *in vitro* studies have shown that homocysteine can influence the cell cycle in vascular smooth muscle cells and in endothelial cells,⁴ we wondered whether the expres-

Serum total homocysteine concentrations (mean μ M/l (SD)) in relation to neuronal expression of cyclin B and cyclin E

	Absent	Present	p Value (ANOVA, Kruskal-Wallis)
Cyclin B	17.1 (8.7)	16.5 (4.5)	0.75
Cyclin E	15.35 (4.2)	18.1 (6.2)	0.045

sion of cell cycle markers in neurons in Alzheimer's disease might be associated with hyperhomocysteinaemia.

We studied the first 60 patients in the Oxford Project to Investigate Memory and Aging (OPTIMA) where both serum homocysteine and postmortem hippocampal tissue were available. Forty eight patients had a histopathological diagnosis of pure Alzheimer's disease, nine had Alzheimer's disease mixed with vascular pathology and three were controls, without CNS pathology. Total serum homocysteine concentrations were determined in blood samples taken at entry of each patient into the study, on average 29.7 (SD 19) months before death.³ The expression of cyclins B and E was studied by immunohistochemical methods⁵ in the nuclei of neurons in the hippocampi by an examiner blind to the diagnosis and to the value of serum homocysteine.

Cyclin B expression in neuronal cell nuclei was found in 50 patients with Alzheimer's disease, and cyclin E expression was detected in 27 patients. The concentration of total serum homocysteine in those patients who expressed cyclin B was no different from that in patients who did not express this cyclin. However, the mean concentration of homocysteine in patients who expressed cyclin E in the brain was 18% higher ($p<0.045$) than that in those who did not express this cyclin (table). Serum vitamin B12 and serum and red blood cell folate concentrations were not significantly different in patients who expressed the cyclins compared with those who did not. To control for the possible influence of other known determinants of serum homocysteine, logistic regression was carried out to see if age, sex, serum creatinine, and serum homocysteine were related to the expression of cyclins B or E. The only significant effect was of homocysteine on expression of cyclin E ($p=0.04$), which was independent of the other factors.

The cell division cycle is a tightly controlled sequence of events that is driven by the sequential nuclear expression and activation of cyclin and cyclin dependent kinase complexes. The nuclear expression of cyclin E is evidence that the neurons have re-entered the cell division cycle whereas expression of cyclin B indicates progression of the cycle to the G2 phase. We suggest that the association of hyperhomocysteinaemia with cyclin E expression, but not with cyclin B expression, may indicate a mitogenic role for homocysteine. The mechanism could be indirect, through the action of homocysteine on the cerebral vasculature, or it might reflect a direct mitogenic action of homocysteine on neurons. Further work is required to test these hypotheses. The rate of atrophy of the hippocampus in Alzheimer's disease is more rapid in patients with increased concentrations of serum homocysteine.³ Thus, if entry into the cell cycle is part of the pathogenic process, then lowering homocysteine concentrations in the blood might slow the progression of the disease.

We thank H Refsum and P Ueland for the homocysteine assays. This work was supported by grants from Bristol-Myers Squibb and Research into Aging.

ZS NAGY
M Z SMITH
M M ESIRI
L BARNETSON
A D SMITH

OPTIMA, University Department of Pharmacology
Mansfield Road, Oxford OX1 3QT, UK and
Department of Neuropathology, Radcliffe Infirmary
NHS Trust, Oxford OX2 6HE, UK

Correspondence to:
Professor A D Smith

Correspondence to: david.smith@pharm.ox.ac.uk

- 1 Nagy Z, Esiri MM, Smith AD. The cell division cycle and the pathophysiology of Alzheimer's disease. *Neuroscience* 1998;87:731-9.
- 2 Refsum H, Ueland P, Nygard O, *et al*. Homocysteine and cardiovascular disease. *Annu Rev Med* 1998;49:31-62.
- 3 Clarke R, Smith AD, Jobst KA, *et al*. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. *Arch Neurol* 1998;55:1449-55.
- 4 Lee ME, Wang H. Homocysteine and hypomethylation: a novel link to vascular disease. *Trend Cardiovasc Med* 1999;9:49-54.
- 5 Nagy Z, Esiri MM, Cato AM, *et al*. Cell cycle markers in the hippocampus in Alzheimer's disease. *Acta Neuropathol* 1997;94:6-15.

CORRESPONDENCE

Visual field defects associated with vigabatrin monotherapy in children

In the December issue of this *Journal* Lawden *et al*¹ found in an adult population receiving vigabatrin (VGB), mostly in association with other antiepileptic drugs, a high prevalence (52%) of visual field defects. These abnormalities were not reversible after discontinuation of VGB therapy.

Since 1990, several authors have reported circumferential narrowing of the visual field with characteristic temporal sparing in patients treated with VGB. Although a visual field defect is the most common cause for discontinuation of VGB therapy, no conclusive data are presently available to explain the pathogenesis of this major side effect.^{1,2} Interestingly, retinal dysfunction has been primarily described in patients receiving VGB in combination with other antiepileptic drugs, whereas only a few cases have been reported in patients treated with VGB as a monotherapy.² Despite increasing attention to this complication, the actual prevalence of visual field defect associated with VGB therapy remains poorly defined. Backstrom *et al* have reported a prevalence of less than 0.10%³ and the Hoechst Marion Roussel Pharmaceutical Company has estimated that the incidence of visual field defect is about 0.15%. Other authors, including Lawden *et al*, however, have recently challenged these data, suggesting a considerably higher prevalence.^{1,2} Such discrepancies can be explained by several factors, including delayed appearance of visual field defects after initiation of VGB treatment (several months up to 7 years), high prevalence of non-symptomatic cases,⁴ and lack of systematic studies. In addition, the often used auto-

mated perimetry (Humphrey field analyser) seems to be significantly less sensitive than the Goldmann kinetic perimetry in detecting visual field defects. These limitations are particularly relevant in assessing the incidence of visual field defects in the paediatric population, given the limited compliance during visual field testing and difficulties of diagnosing visual symptoms in very young children.

We have followed up 13 paediatric patients treated with VGB monotherapy, whom we have systematically screened to detect visual field defects associated with this therapy, even in the absence of visual symptoms. Our patients were aged 5 to 16 years (mean 10.5 (SD 3.8) years) and received VGB monotherapy for localisation related epilepsy during an average period of 41 (SD 18) months (range 8-64 months). In all cases, significant improvement of seizure control was obtained. Routine visual field examinations were not performed until the first reports of visual field defects associated with VGB treatment were published.⁵ Since 1997, systematic kinetic perimetry was performed in all patients and careful attention was paid to identify visual symptoms during regular follow up visits. Clinical evidence of impaired peripheral vision was not apparent in any of our patients. However 8/13 (62%) patients were diagnosed with retinal dysfunction characterised by moderate, concentric narrowing of the visual field with temporal sparing in six patients and severe narrowing of the visual field without temporal sparing in two patients; VGB therapy was discontinued in all patients with visual field defects. Partial recovery after discontinuation of the therapy was not found in any of our patients. By contrast with the above results, no evidence of visual field defects was diagnosed with the Goldmann technique, in 12 control patients with localisation related epilepsy treated with carbamazepine monotherapy.

To our knowledge, these data constitute the largest reported series of VGB monotherapy in the paediatric population. Our results show that, despite severe limitations in diagnosing visual field defects in children, systematic screening can reliably detect visual field anomalies in the paediatric population. Routine screening should be performed even in non-symptomatic children. Similarly to recent reports in the adult population,² our data show that visual field defects are not limited to patients receiving VGB in combination with other antiepileptic drugs but can develop also in children on VGB monotherapy. Our series data in a paediatric population are similar to the data reported by Lawden *et al* in an adult population. They also suggest an overall prevalence of visual field defects considerably higher than previously reported, and show that retinal lesions associated with VGB therapy are not reversible.

ANNA LUCHETTI
ALESSANDRA AMADI
GIUSEPPE GOBBI

Unità Operativa di Neuropsichiatria Infantile,
Ospedale Maggiore, CA Pizzardi, Largo Nigrisoli 2,
40133 Bologna, Italy

GIANNA BERTANI
Unità Operativa di Neuropsichiatria Infantile,
Arcispedale S.Maria Nuova, Viale Risorgimento 80,
42100 Reggio Emilia, Italy

Correspondence to: Dr Giuseppe Gobbi
Giuseppe.Gobbi@ausl.bologna.it

- 1 Lawden MC, Eke T, Degg C, *et al*. Visual field defects associated with vigabatrin therapy. *J Neurol Neurosurg Psychiatry* 1999;67:716-22.

- 2 Kalviainen R, Nousiainen I, Mantjarvi M, *et al*. Vigabatrin, a GABAergic antiepileptic drug, causes concentric visual field defects. *Neurology* 1999;53:922-6.
- 3 Backstrom JT, Hinkle RL, Flicker MR. Severe persistent visual field constriction associated with vigabatrin. Manufacturers have started several studies. *BMJ* 1997;314:1694-5.
- 4 Arndt CF, Derambure P, Defoort-Dhellemmes S, *et al*. Outer retinal dysfunction in patients treated with vigabatrin. *Neurology* 1999;52:1201-5.
- 5 Eke T, Talbot JF, Lawden MC. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997;314:180-1.

Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies

We read with much interest the article by Giovannoni *et al*¹ depicting the clinical entity that goes under the name of "hedonistic homeostatic dysregulation" in parkinsonian patients.

Obviously, the scientific background that allowed the authors to disentangle the syndrome includes two basic concepts: (1) exogenous dopaminergic stimulation and its fluctuations can and do affect mood in the parkinsonian patient and (2) the target of this influence is the reward related dopamine system, arising from the ventral tegmental area of the mesencephalon and innervating wide regions of the frontal and temporal lobes. Nowadays, these concepts may seem trivial, but they were certainly not so in the late 1980s, when I coauthored two papers that appeared in this *Journal*.^{2,3} Contrary to Giovannoni *et al*,¹ I do think it fair to remind readers of these articles, because they may help the interested reader to understand more of the long story of Parkinson's disease, dopamine, and depression. In the 1986 paper,² we provided the first controlled demonstration that a state of dopaminergic hypoactivity (end of dose deterioration) was significantly ($p < 0.05$) associated with a negative mood swing. The control was represented by patients with advanced rheumatoid arthritis whose motor ability fluctuated predictably because of their joint stiffness on awakening. Patients with Parkinson's disease who were steadily depressed (they were depressed even in their mobile periods), were significantly ($p < 0.05$) less prone to a further mood worsening during immobility than patients who did not have a steady depression. We interpreted this as evidence that the dopaminergic system implicated in mood regulation was so severely affected in the former group, to prevent significant fluctuation. But because the motor status of these patients did fluctuate, the system should have been non-nigrostriatal—that is, mesocorticolimbic. These findings, or their essence, were replicated by independent investigators.⁴ In the second paper,³ we used an amphetamine-like compound—methylphenidate—to test the functionality of the reward or pleasure related dopamine system in patients with Parkinson's disease with major depression, in non-depressed patients with Parkinson's disease, in non-Parkinson's disease patients with major depression, and in age matched healthy controls. The methylphenidate test is used by biological psychiatrists, including studies of people addicted to central stimulants, which relates to the thesis of Giovannoni *et al*.¹ The overall result was that patients with Parkinson's disease with major depression showed characteristically a poor euphoriant response to the intravenous injection of the drug. The