menstrual bleeding there is a sudden fall in circulating levels of progesterone and oestradiol. Both sex steroids have numerous regulatory effects on the immune system, including an influence on T cell populations, and the production of cytokines.^{4,5}

Inflammatory cytokines, or so called Th1 cytokines, such as INF- γ , tumour necrosis factor- α (TNF- α), and interleukins 1 and 2 (IL-1 and IL-2), seem to play a key part in the generation of exacerbations in multiple sclerosis.⁶ Pathways through which sex steroids influence the immune system are complex and incompletely understood. Oestrogens may inhibit the release of Th1 cytokines, such as IL-1 and TNF- α , whereas progesterone may enhance the release of Th2 cytokines, which inhibit the production and activity of the Th1 cytokines.⁷⁻⁹ Thus the abrupt withdrawal of progesterone and oestradiol in the premenstrual phase may shift the balance in favour of the production of inflammatory Th1 cytokines. Also, other hormones, such as inhibin, may contribute to this effect. The circulating concentration of inhibin, a hormone which decreases INF- γ production, also sharply declines just before the menstruation.¹⁰ Changes in concentrations of circulating sex hormones during the menstrual cycle were also found to influence disease activity in other putative autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus, and autoimmune thyroid disease.^{5,11,12}

An important question that needs to be investigated is whether the premenstrual period is an independent risk factor for exacerbations in the whole female multiple sclerosis population. This should be examined by a large prospective study. Unravelling the roles of sex hormones in the immune system and cytokine network that may regulate disease activity in multiple sclerosis may provide clues for the development of new therapeutic strategies.

ANNEKE ZORGDRAGER
JACQUES DE KEYSER

Department of Neurology, Academisch Ziekenhuis
Groningen, Groningen, The Netherlands

Correspondence to: Dr A Zorgdrager, Department of Neurology, Academisch Ziekenhuis Groningen, Hanzplein 1, PO Box 30.001, 9700 RB Groningen, The Netherlands. Telephone 0031 50 3612430; fax 0031 50 3611707; email a.n.zorgdrager@neuro.azg.nl

- 1 Panitch HS. Influence of infection on exacerbations of multiple sclerosis. *Ann Neurol* 1994;36:S25-8.
- 2 Abramsky O. Pregnancy and multiple sclerosis. *Ann Neurol* 1994;36:S38-41.
- 3 Zorgdrager A, De Keyser J. Menstrually related worsening of symptoms in multiple sclerosis. *J Neurol Sci* 1997;149:95-7.
- 4 Ahmed SA, Penhale WJ, Talal N. Sex hormones, immune responses, and autoimmune diseases. Mechanisms of sex hormone action. *Am J Pathol* 1985;121:531-51.
- 5 Homo-Delarche F, Fitzpatrick F, Christeff N, et al. Sex steroids, glucocorticoids, stress and

autoimmunity. *J Steroid Biochem Molec Biol* 1992;40:619-37.

- 6 Owens T, Sriram S. The immunology of multiple sclerosis and its animal model, experimental allergic encephalomyelitis. *Neurol Clin* 1995;13:51-73.
- 7 Cutolo M, Sulli A, Serio B, et al. Estrogens, the immune response and autoimmunity. *Clin Exp Rheumatol* 1995;13:217-26.
- 8 Pacifici R. Estrogen, cytokines, and pathogenesis of postmenopausal osteoporosis. *J Bone Miner Res* 1996;11:1043-51.
- 9 Piccinini M-P, Giudizi M-G, Biagiotti R, et al. Progesterone favors the development of human T helper cells producing Th2-type cytokines and promotes both IL-4 production and membrane CD30 expression in established Th1 cell clones. *J Immunol* 1995;155:128-33.
- 10 Petraglia F, Sacerdote P, Cossarizza A, et al. Inhibin and activin modulate human monocyte chemotaxis and human lymphocyte interferon- γ production. *J Clin Endocrinol Metab* 1991;72:496-502.
- 11 Latman NS. Relation of menstrual cycle phase to symptoms of rheumatoid arthritis. *Am J Med* 1983;74:957-60.
- 12 Steinberg AD, Steinberg BJ. Lupus disease activity associated with menstrual cycle. *J Rheumatol* 1985;12:816-7.

CORRESPONDENCE

Autonomic effects of selegiline: possible cardiovascular toxicity in Parkinson's disease

(1)

We read with interest the article by Churchyard *et al*¹ showing that selegiline in combination with levodopa was associated with significant impairment of the normal reflex responses controlling blood pressure to head up tilt and standing. It was suggested by the authors that this could be one explanation of the finding of increased mortality in the combined levodopa/selegiline arm of the Parkinson's Disease Research Group of the United Kingdom trial.² We are currently conducting a study investigating the cardiovascular reflexes in patients recruited from a community disease register for Parkinson's disease, diagnosis being based on identical clinical diagnostic criteria to the reported study. Patients were excluded from the study if they were known to have diseases associated with impaired autonomic system function or if they were currently being treated with drugs other than those for Parkinson's disease. We have identified 27 such patients, five receiving selegiline and levodopa and 22 receiving levodopa. With similar techniques and equipment as the authors we have measured orthostatic blood pressure at 1 minute, Valsalva ratio, and heart rate on standing (30:15 ratio). Age, sex, duration of disease, Webster scale, and daily levodopa dose did not differ significantly between the group of patients on levodopa alone and on levodopa and sel-

egiline combined (table). There was no significant difference in the results of autonomic function testing between the two groups with analysis of variance (ANOVA) and *t* tests. Both groups of patients showed falls in blood pressure on standing and this did not seem to be more pronounced in the group on levodopa plus selegiline compared with patients on levodopa alone. This finding is surprising given the much lower dose of levodopa prescribed in our study compared with that of Churchyard *et al*. However, our failure to show significant hypotensive interaction between selegiline and levodopa may have resulted from the lower dose of levodopa prescribed in our study. We did not specifically look at blood pressure changes during 45° head up tilt. As yet we have not been able to retest patients in whom selegiline has been withdrawn to see if any significant changes become apparent. In view of the small sample sizes reported by Churchyard *et al* and our own study, we think that both sets of results should be interpreted with caution. In elderly patients with Parkinson's disease even modest doses of levodopa seem to be associated with orthostatic hypotension. It seems unlikely that the additional hypotensive effect of selegiline could be the sole explanation of the apparent increased mortality with levodopa and selegiline compared with levodopa alone.

JOHN COYLE
PETER HOBSON
JOLYON MEARA

University Department of Geriatric Medicine, Glan
Clwyd District General Hospital, Rhyl, Denbighshire
LL18 5UJ, UK

Correspondence to: Dr J Meara, University Department of Geriatric Medicine, Glan Clwyd District General Hospital, Rhyl, Denbighshire LL18 5UJ, UK.

- 1 Churchyard A, Mathias CJ, Boonkongchuen P, et al. Autonomic effects of selegiline: possible cardiovascular toxicity in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997;63:228-34.
- 2 Lees AJ, on behalf of the Parkinson's Disease Research Group of the UK. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995;311:1602-7.

(2)

We have read with great interest the article by Churchyard *et al*¹ that appeared in the *Journal*. There are several issues that we comment on.

The study design is not scientifically sound: the trial is not randomised, the number of patients in the two groups is unequal, and half of the patients were selected from an earlier study.² According to the authors the two groups were matched for age, duration, and severity of the disease, and the dose of levodopa. Due to the study design the patients could not, however, be matched according to the autonomic functions, although there were no significant differences in the occurrence of clinical postural dizziness. The change in the systolic blood pressure after standing was, however, significantly lower in the selegiline group (group II) after the withdrawal than in the group receiving only levodopa (group I). Also one patient in group I had a clear hypertensive reaction (systolic blood pressure >200 mm Hg) while standing. This suggests that the autonomic function in group II even without selegiline was more compromised than in the group I, thus showing a selection bias.

It is not, however, a new finding that orthostatic hypotension could occur when

Table 1 Mean (SEM) median indices for patients taking levodopa only or levodopa and selegiline

	Levodopa (n=22)	Selegiline (n=5)
Age (y)	71.7 (1.7) 72	64.8 (6.6) 66
Duration (y)	6.6 (0.9) 5.5	7.0 (1.9) 5.0
Webster scale	13.4 (1.4) 15	11.4 (2.1) 10
Daily selegiline dose (mg) (mean duration 7 y)		10
Daily levodopa dose (mg)	433 (43) 350	560 (254) 400
Supine systolic BP	158.8 (5.3) 158	143.6 (7.6) 145
Standing systolic BP	147.7 (5.9) 143	133.6 (10.8) 143
% Change systolic BP	-7.6 (-1.6) -8.4	-7.5 (-3.1) -6.5
30:15 Ratio	1.03 (0.01) 1.02	1.04 (0.02) 1.06
Valsalva ratio	1.16 (0.03) 1.15	1.2 (0.01) 1.19

selegiline and levodopa are given together. Orthostatic hypotension is often found in late stage Parkinson's disease due to autonomic disturbances.³ All dopaminergic drugs such as levodopa or dopamine agonists have been shown to cause orthostatic hypotension.⁴ In a recent double blind study Turkka *et al*⁵ prospectively followed up patients in a double blind study measuring autonomic function with a similar method to Churchyard *et al*¹ for several years. They found that with time there was significantly more orthostatic hypotension assessed with the tilt test in the selegiline plus levodopa group than placebo plus levodopa group. However, only two out of 27 patients in the selegiline group fulfilled the criteria of orthostatic hypotension.

The mode of action of orthostatic hypotension with dopaminergic drugs is not clear. Selegiline is known to potentiate the therapeutic effects of levodopa but also its adverse effects if the dose of levodopa is not reduced sufficiently.⁶ The authors claim that selegiline would impair the noradrenaline and heart rate responses to tilt although no significant changes were detected between the groups. The authors make hasty conclusions that selegiline would be cardiotoxic with no scientific verification. If a drug causes orthostatic hypotension it does not mean that the drug would be cardiotoxic!

Furthermore, the authors showed that the clinical condition of the patients deteriorated considerably after withdrawal of selegiline. As the disability was considerably worse after the withdrawal than during selegiline treatment, the effect of adequate dopaminergic medication on cardiovascular responses remains unknown. It is possible that adding a sufficient amount of dopaminergic medication to group II after withdrawal of selegiline would cause similar orthostatic hypotension to that found when selegiline was combined with levodopa. Indeed, Kaufman *et al*⁷ analysed patients with Parkinson's disease with orthostatic hypotension and found no significant difference between patients treated with levodopa, dopamine agonist, or the combination of selegiline and levodopa.

Finally, the authors suggest that their findings would be related to the metabolites of selegiline. The authors did not take into account that these amphetamine metabolites are of levoform. Furthermore, d-methamphetamine or d-amphetamine often cause increases of blood pressure, not hypotension.⁸ Similarly, there is a dose proportional increase of blood pressure in rats caused by d-p-hydroxy amphetamine or d-p-hydroxy-norephedrine.⁹ The authors imply that selegiline would cause withdrawal effects in humans and refer to an experimental study on rats (³³ cited by Churchyard *et al*¹). The authors also suggest that selegiline loses its selectivity during treatment. A postmortem study showed, however, that there was no increase of monoamine oxidase-A inhibition along with long term selegiline treatment.¹⁰

ESA HEINONEN

Orion Pharma, Clinical Research, Turku, Finland

VILHO MYLLYLÄ

Department of Neurology, University of Oulu, Oulu, Finland

Correspondence to: Dr Esa Heinonen, PO Box 425, 20101 Turku, Finland. Telephone 00358 2 2727 383; fax 00358 2 2727 432.

1 Churchyard A, Mathias CJ, Boonkongchuen P, *et al*. Autonomic effects of selegiline: possible cardiovascular toxicity in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997;63:228-34.

- 2 Lees AJ. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995;311:1602-7.
- 3 Meco G, Paratesi L, Bonifani V. Cardiovascular reflexes and autonomic dysfunction in Parkinson's disease. *J Neurol* 1991;238:195-9.
- 4 Schoenberger JA. Drug-induced orthostatic hypotension. *Drug Saf* 1991;6:402-7.
- 5 Turkka J, Suominen K, Tolonen U, *et al*. Selegiline diminishes cardiovascular autonomic responses in Parkinson's disease. *Neurology* 1997;48:662-7.
- 6 Heinonen EH, Rinne UK. Selegiline in the treatment of Parkinson's disease. *Acta Neurol Scand* 1989;126:103-11.
- 7 Kaufmann H, Nouri S, Caro S, *et al*. Orthostatic intolerance in Parkinson's disease. *Mov Disord* 1997;12(suppl 1):P526.
- 8 Angrist B, Corwin J, Bartlik B, *et al*. Early pharmacokinetics and clinical effects of oral d-amphetamine in normal subjects. *Biol Psychiatry* 1987;22:1357-68.
- 9 Simpson LL. Blood pressure and heart rate responses evoked by p-hydroxy amphetamine and by p-hydroxynorephedrine. I The relationship between evoked responses and plasma levels of drug. *J Pharmacol Exp Ther* 1979;211:225-30.
- 10 Riederer P, Reynolds GP. Deprenyl is a selective inhibitor of brain MAO-B in the long-term treatment of Parkinson's disease. *Br J Clin Pharmacol* 1980;9:98-9.

The authors' reply:

Heinonen and Myllylä have raised several issues relating to our recent article which appeared in *J Neurol Neurosurg Psychiatry*.¹ As they note, the study, which examined autonomic function in those on long term treatment (mean >5 years), was of necessity not randomised. However, selection bias was minimised by recruitment of all outpatients on levodopa and selegiline or levodopa without selegiline within a given time and regardless of the presence or absence of symptoms suggestive of autonomic dysfunction. That there was no bias towards more severely affected cases being placed on selegiline is strongly suggested by the excellent match between the two groups for age, duration and severity of disease, and the dose of levodopa and the greater frequency of symptomatic postural dizziness in those on levodopa alone. Moreover, as noted by Heinonen and Myllylä, the combination of selegiline and levodopa was also associated with a higher incidence of postural hypotension than levodopa and placebo in a prospective, randomised double blind study.² Heinonen and Myllylä note that the percentage change in systolic blood pressure, but not the absolute levels, was lower in those previously on selegiline and levodopa three months after withdrawal of selegiline than in those originally on levodopa alone. However, both the standing systolic blood pressure and the percentage drop were greater than when patients were taking selegiline and levodopa. That is, the hypotensive effects of standing had improved three months after stopping selegiline even though the average daily dose of levodopa had been increased (not significant) and seven (44%) patients required addition of the potentially hypotensive ergolene pergolide. This suggests that the orthostatic effect was specific for selegiline and levodopa rather than a non-specific consequence of dopaminergic treatment itself. Therefore, we think that our finding that selegiline and levodopa cause orthostatic hypotension is robust and represents an unwanted and potentially dangerous drug interaction.

Coyle, *et al* examined standing systolic blood pressure, Valsalva ratio, and 30:15 ratio in 22 patients on levodopa alone and five on

selegiline and levodopa. They found that standing precipitated a small and asymptomatic fall in systolic blood pressure that was similar in both groups and by contrast with our finding that levodopa and selegiline caused a greater drop in standing systolic blood pressure than levodopa alone.¹ However, the number of those on selegiline and levodopa was small and, as Coyle *et al* note, the daily dose of levodopa was lower. Moreover, although both groups were apparently matched, the mean age of those on levodopa alone was seven years more than those on the two drugs and the SEM of age of those taking selegiline and levodopa was 10%, implying a much greater age range in this group and so raising the possibility that increased orthostatic hypotension in those on levodopa alone as a result of aging³ might have exerted a confounding influence on their data.

Coyle *et al* reasonably caution that autonomic function has been examined in only a few published cases. Collectively, we¹ and Turkka *et al*⁵ have studied 43 patients on levodopa and selegiline with both groups finding that the combination of drugs was associated with greater orthostatic hypotension than levodopa alone. In a separate study of 20 patients on selegiline (unpublished data) we have again found a similar impairment of cardiovascular reflexes which occurred as a result of selegiline and levodopa treatment. Thus, we think that our findings indicate that the combination of selegiline and levodopa impairs cardiovascular control in at least some and perhaps even a majority of patients with moderately advanced or severe Parkinson's disease.

We agree with Heinonen and Myllylä that the causes of orthostatic hypotension induced by selegiline and levodopa are unknown. We considered two potential causes: an amphetamine effect or increasing inhibition of monoamine oxidase-type A which might be expected to increase plasma concentrations of the false transmitter tyramine, which also causes orthostatic hypotension.⁴ Selegiline may lose some of its selectivity for monoamine oxidase type B at high doses or with chronic treatment at <10 mg/day.⁵⁻⁷ Riederer *et al* found that >65% of monoamine oxidase type A activity was inhibited by treatment with selegiline at 5-10 mg/day in the brains of seven patients with Parkinson's disease and noted that the degree of inhibition of monoamine oxidase type A seemed to rise with increasing duration of treatment.⁸ Selegiline comprises the l-isomer of deprenyl and is thought to be largely metabolised to l-amphetamine and l-metamphetamine⁹ which have less potent cardiovascular toxicity than the d-isomers. Although amphetamines cause supine hypertension, they have also caused orthostatic hypotension by impairing sympathetic function in humans.¹⁰ To our knowledge cerebral and plasma concentrations of the l-isomers and d-isomers of amphetamine have not been measured in those on long term selegiline treatment. Thus the possibility that high cerebral or plasma concentrations of l-amphetamine and l-metamphetamine sufficient to cause toxic cardiovascular effects as a result of long term treatment with selegiline and levodopa cannot be excluded. In the submitted study of 20 patients on selegiline already referred to we found that the impaired cardiovascular reflexes due to selegiline and levodopa treatment normalised within four to seven days of stopping selegiline. This time course was consistent with either an amphetamine effect

or loss of selectivity for monoamine oxidase type B resulting in excess plasma tyramine. However, in this study selegiline seemed to cause supine hypertension as well as orthostatic hypotension. This combination would be consistent with either an amphetamine or a tyramine effect.

The failure of patients with severe orthostatic hypotension induced by selegiline and levodopa to develop a compensatory tachycardia indicates impairment of cardiovascular reflexes¹ and as such is consistent with significant, albeit reversible, drug toxicity by whatever mechanism.

ANDREW CHURCHYARD
ANDREW LEES
CHRISTOPHER J MATHIAS

- Churchyard A, Mathias CJ, Lees AJ. Autonomic effects of selegiline possible cardiovascular toxicity in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997;63:228-34.
- Turkka J, Suominen K, Tolonen U, et al. Selegiline diminishes cardiovascular autonomic responses in Parkinson's disease. *Neurology* 1997;48:662-7.
- Johnson RH. Aging and the autonomic system. In: Bannister RB, Mathias CJ, eds. *Autonomic failure. A textbook of clinical disorders of the autonomic nervous system*. 3rd ed. Oxford: Oxford University Press, 1992.
- McDaniel KD. Clinical pharmacology of monoamine oxidase inhibitors. *Clin Neuropharmacol* 1986;9:207-34.
- Waldmeier PC, Felner AE. Deprenil: loss of selectivity for inhibition of B-type MAO after repeated treatment. *Biochem Pharmacol* 1978;27:801-2.
- Ekstedt B, Magyar K, Knoll J. Does the B form selective monoamine oxidase inhibitor lose selectivity by long term treatment? *Biochem Pharmacol* 1979;28:919-23.
- Gelowitz DL, Richardson JS, Wishart TB, et al. Chronic 1-deprenyl or 1-amphetamine: equal cognitive enhancement, unequal MAO inhibition. *Pharmacol Biochem Behav* 1994;47:41-5.
- Riederer P, Youdim MBH, Rausch WD, et al. On the mode of action of 1-deprenyl in the human nervous system. *J Neural Transm Gen Sect* 1978;43:17-26.
- Reynolds GP, Elsworth JD, Blau K, et al. Deprenyl is metabolised to metamphetamine and amphetamine in man. *Br J Clin Pharmacol* 1978;6:542-5.
- Gill JR, Mason DT, Bartter F. Effects of hydroxy amphetamine on the function of the sympathetic nervous system in normotensive subjects. *J Pharmacol Exp Ther* 1967;155:288-95.

Idiopathic generalised epilepsy in adults manifested by phantom absences, generalised tonic-clonic seizures, and frequent absence status

I read with interest the report by Panayiotopoulos *et al.*¹ Their series recalled a 58 year old man who presented for evaluation after several episodes presumed to be complex partial status epilepticus. His neurological history was remarkable only for two convulsions in his late teens which led to his discharge from the armed forces. He did not recall whether these seizures were related to sleep deprivation or alcohol withdrawal. He did not recall being informed of seizures, staring spells, or other paroxysmal events as a child. He denied a family history of seizures or other neurological diseases. He was treated briefly with phenytoin, but was free of seizures and took no anticonvulsant drugs for almost 40 years, when he began to experience episodic confusion lasting for hours. Interictal EEGs were reported to show spike wave discharges. Brain MRI was normal. He was treated with various combinations of phenytoin, carbamazepine, phenobarbitone, and primidone, which did not prevent these confusional episodes. Video EEG monitoring

after withdrawal of all antiseizure medications showed frequent bursts of 3-3.5 Hz spike wave activity. Hyperventilation produced clinical and electrographic seizures lasting ≥ 8 minutes at a time, and terminating spontaneously. The patient became confused, was unable to follow simple commands, answer questions, or repeat simple phrases. Electrographically, these seizures consisted of bisynchronous, frontally predominant spike wave discharges which began at 3.5 Hz but slowed to 2.5 Hz over several minutes. At the end of each seizure, the patient was immediately alert and able to follow commands, converse, and repeat. Treatment with divalproex (750 mg/day) abolished the seizures and the interictal EEG abnormalities for four years. The patient did not wish to attempt withdrawal from divalproex, and was returned to the care of his family physician.

I would like to ask the authors whether their patients manifested an EEG or clinical response to hyperventilation.

THOMAS P BLECK
Department of Neurological Surgery and Internal Medicine, Neuroscience Intensive Care Unit, The University of Virginia, VA, USA

- C P Panayiotopoulos, M Koutroumanidis, S Giannakodimos, et al. Idiopathic generalised epilepsy in adults manifested by phantom absences, generalised tonic-clonic seizures, and frequent absence status. *J Neurol Neurosurg Psychiatry* 1997;63:622-7.

Panayiotopoulos *et al* reply:

We thank Bleck for vividly illustrating the challenging diagnostic and management problems of these patients that were among the main purposes of our report. His patient, like ours, had infrequent generalised tonic clonic seizures with onset in the late teens and frequent episodes of absence status that was misdiagnosed as complex partial status epilepticus. Also, he probably had phantom absences during interictal generalised 3-3.5 Hz spike and slow wave discharges but this needs documentation with breath counting or other means of testing for mild impairment of cognition. Similarly to our cases, he was also erroneously treated with phenytoin, carbamazepine, and barbiturates for many years and seizures stopped only when appropriate medication of divalproex was prescribed. He was fortunate not to receive vigabatrin, which exacerbates absences and absence status.

The only difference from our cases is that Bleck's patient had prolonged, 8 minute, severe absence seizures provoked by hyperventilation after withdrawal of all antiseizure medication. Although briefer, this was similar to the absence status in our patients; this severe electroclinical state was documented only during spontaneous absence status, not during hyperventilation. However, in all patients over-breathing increased the generalised 3-4 Hz spike or polyspike and slow wave discharges that were often associated with mild impairment of cognition, shown with errors of breath counting. Hyperventilation was the only means of inducing generalised 3-4 Hz spike and slow wave discharges in some of the patients whose resting EEG could be normal. This is in accordance with the provoking effect of hyperventilation on absences of the idiopathic generalised epilepsies.

C P PANAYIOTOPOULOS
M KOUTROUMANIDIS
S GIANNAKODIMOS
A AGATHONIKOU

BOOK REVIEWS

The Neuropathology of Dementia.

Edited by MARGARET M ESIRI and JAMES H MORRIS. (Pp 440; £75.00.) Published by Cambridge University Press, Cambridge. 1997. ISBN 0-521-43311-8.

This distinguished pair of Oxford neuropathologists offer a new book to the "pathologist faced with the task of determining the cause of dementia in cases requiring post-mortem diagnosis". They are credited with editorship; actually, they have written 11 chapters and two appendices, among them those chapters which deal with the pathological processes which account for 90% of adult dementia (Alzheimer's disease, vascular disease, and Lewy body disease). For the remaining eight chapters and appendix, Professor Esiri and Dr Morris recruited acknowledged experts.

After an introductory chapter on dementia, which describes the clinical syndrome and describes its neuroanatomical basis, there are two chapters in which Esiri and Morris define the practical approach to the pathological diagnosis of dementia. The first of these chapters describes (and illustrates diagrammatically) the neuroanatomical structures which are particularly pertinent to cases of dementia. The diagrams of neural connectivity in the hippocampus and neocortex may daunt the general pathologist, but the chapter provides a useful summary of pathological processes which affect each anatomical region of the brain; that is to say, it offers a regional approach to the differential diagnosis of dementia. The second of these chapters gives instruction on the conduct of the post-mortem in a case of dementia, details the observations which should be made on the unfixed brain at the time of postmortem, and on the fixed brain, and provides a scheme for the selection of tissue blocks and histological stains.

The rest of the book is composed of chapters which are dedicated to individual causes of dementia, starting with the commonest diseases: Alzheimer's disease, vascular disease, and Lewy body disease. The very numerous rare causes of dementia are all discussed in subsequent chapters, which include adequately comprehensive and up-to-date accounts of aetiology and pathogenic mechanisms, but manage to retain the practical perspective; a mark of successful editorship. I should emphasise that this book is not simply a practical manual although it largely succeeds in that respect. It succeeds also in taking a common sense approach to issues which are controversial among neuropathologists. The general pathologist who turns to this book will receive sound advice on such matters as the pathological diagnostic criteria of Alzheimer's disease and its distinction from age related changes, on the relation of head injury to the pathogenesis of Alzheimer's disease, and on the range of clinical and pathological phenotypes which are included