LETTERS TO THE EDITOR

A simple model to explain the motor fluctuations seen in Parkinson's disease

Confusion and controversy surround the cause of motor fluctuations in Parkinson's disease. Loss of dopamine storage capacity is the widely accepted explanation. The paper by Rodriguez *et al*¹ has finally disproved this popular hypothesis. The motor responses for apomorphine and levodopa are identical. Apomorphine is not biotransformed to be active or stored in the brain excluding change in the storage capacity as the explanation. Neither are there, in this study, any significant differences in the motor responses of new patients and patients treated with levodopa, eliminating any change in pharmacodynamics or pharmacokinetics as the explanation.

Fabbrini *et al*² and Bravi *et al*³ however, have shown that the duration of motor response from "on" to "off" for levodopa and apomorphine respectively is shorter in patients with motor fluctuations. Because of this they have concluded that postjunctional mechanisms possibly due to treatment are responsible for the motor fluctuations in Parkinson's disease.

I think that this conclusion is incorrect. I suggest an alternative explanation based on the following model, which satisfactorily explains the changes in motor performance with progression of Parkinson's disease. The model shows that these changes are directly determined by the severity of the dopaminergic deficit, about which there is no disagreement. It requires no change in the pharmacology of the response to levodopa, no change in storage with disease duration and progression, and no postjunctional changes to explain the phenomena.

The figure represents two stages of Parkinson's disease; early stable response and end of dose deterioration. It assumes a constant amplitude and duration of central dopaminergic stimulation due to a fixed

dose of levodopa throughout the course of the disease. This is entirely dependent on the plasma concentration of levodopa with no storage of dopamine. A threshold of central dopaminergic stimulation for "on" is assumed as this corresponds to clinical experience. Variable amounts of motor response above this threshold are represented. This may be clinically apparent in some patients who get a better "on" with a larger dose; in others with early disease it may be "concealed" because the dose of levodopa is sufficient to achieve maximum "on". The amount of central dopaminergic stimulation varies during this period of stable motor response due to the short plasma half life of levodopa, but because in early disease the amount of dopaminergic stimulation is always above threshold, wearing off is not apparent. The levodopa "dose response" curve remains constant throughout the course of the illness.

This model explains the observations of Fabbrini *et al*,² Kempster *et al*,⁴ and Rodriguez *et al*,¹ and is able to reconcile them. It shows an increased amplitude of motor response with progression of disease. This is due to the greater difference between disability "on" and "off" with increasing disease duration.

There is no change in the total duration of motor response from "off" to "off", which Kempster *et al*⁴ showed to be the case. It should be stressed that the duration of motor response measured in this instance is from "off" to "off" and not from "on" to "off".

With disease progression and the development of motor fluctuations, there is faster wearing off from "on". This is due to the differences in the amount of dopaminergic stimulation above the threshold. In early disease this is substantial and "concealed" so that no wearing off between doses is apparent but with disease progression the amount of dopaminergic stimulation above the threshold is less so that wearing off of the response appears and occurs sooner in those patients with motor fluctuations. The rate of wearing off is unchanged, however. This agrees with the data of Bravi *et al*³ shown in fig 2 of their paper in which the slopes of the wearing off from uncomplicated patients, wearing off, and on-off fluctuators are identical. The model also explains the asymmet-

ric motor responses shown by Rodriguez *et al*.¹ The latency to "on" is longer on the more affected side because more dopaminergic stimulation is required to reach "on" and the rate of increase of dopaminergic stimulation is identical for the two sides. The more severely affected side switches off sooner for the same reason that patients with motor fluctuations wear off before those with stable responses.

No change in post-synaptic receptor binding or otherwise is required to explain the motor fluctuations that inevitably develop in Parkinson's disease. They are an inevitable consequence of progression of the dopaminergic deficit and the short half life of levodopa. This model suggests, therefore, that the duration of levodopa treatment is irrelevant to the development of motor fluctuations. This implies that withholding levodopa for as long as possible may deprive patients of a period of benefit without complications.

D E BATEMAN
10 The Tynning,
Widcombe,
Bath BA2 6AL, UK

- 1 Rodriguez M, Lera G, Vaamonde J, Luguin MR, Obeso JA. Motor response to apomorphine and levodopa in asymmetric Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1994;57:562-6.
- 2 Fabbrini G, Mouradian MM, Juncos JJ, Schlegel J, Mohr E, Chase TN. Motor fluctuations in Parkinson's disease: central pathophysiological mechanisms, part 1. *Ann Neurol* 1988;24:366-71.
- 3 Bravi D, Mouradian MM, Roberts JW, Davis TL, Sohn YH, Chase TN. Wearing off fluctuations in Parkinson's disease: contribution of postsynaptic mechanisms. *Ann Neurol* 1994;36:24-31.
- 4 Kempster PA, Frankel JP, Bovington M, Webster R, Lees AJ, Stern GM. Levodopa peripheral pharmacokinetics and duration of motor response in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1989;52:718-23.

Severe intraventricular haemorrhage shown by computed tomography as an unusual manifestation of Wernicke's encephalopathy

The most common pattern of presentation of acute Wernicke's encephalopathy is an altered conscious state.¹ The full clinical triad of Wernicke's encephalopathy (ophthalmoplegia, gait ataxia, and abnormal mental state) is the exception rather than the rule (Harper *et al*, 1986, cited in Naidoo *et al*).¹ We report on the case of a non-alcoholic patient with cancer who was shown to have Wernicke's encephalopathy on necropsy. She died of massive periventricular haemorrhage extending intraventricularly, a very uncommon manifestation of Wernicke's encephalopathy.

A 59 year old non-alcoholic adipose woman was admitted to the University Hospital of Gynaecology in an acute, confused state that had developed over two days. She had had a vaginal hysterectomy three and a half years previously for cancer of the endometrium. A local recurrence of cancer six months later was treated with radiation therapy. Another tumour recurrence two years later required surgery followed by intermittent combination chemotherapy (epirubicin, carboplatin, and cyclophosphamide) for six months. Five weeks before admission recurrence of cancer was diagnosed. A low anterior resection of the rectosigmoid with colorectal anastomosis

Two stages of Parkinson's disease: stable response and end of dose deterioration. The "dose response" curve of dopaminergic stimulation is unchanged but starts from a lower baseline due to disease progression.

(a) Demonstration of haemorrhage by CT (without contrast) in the third ventricle, ambient, and quadrigeminal cistern. (b) Coronal section showed a pronounced haemorrhage in the third ventricle (arrow). In addition, small areas of haemorrhagic discoloration in cortical/subcortical regions secondary to agonal raised intracranial pressure are shown. (c) A necrotising haemorrhagic lesion in the floor of the fourth ventricle (arrow), small areas of haemorrhagic necrosis in cortical regions secondary to agonal raised intracranial pressure, and subarachnoid haemorrhage, especially in the basal cisterns and the leptomeninges of the cerebellar vermis secondary to intraventricular haemorrhage.

and cystectomy with construction of an ileal conduit were performed. Two and a half weeks before admission the patient developed a rectovaginal fistula; the rectum and sigmoid colon were resected and an end colostomy and another ileal conduit were constructed. Oesophagogastroscopy, performed because of vomiting four days before admission, showed candidiasis of the oesophagus. Neurological examination showed that the patient was disoriented in time, had a right sided abducens paresis, horizontal gaze evoked nystagmus to the left, and a vertical gaze evoked nystagmus upward. The tendon reflexes were normal. She had no paresis of the extremities, but slight dysmetria of the arms and legs. There were no sensory abnormalities. Routine laboratory tests were normal except for serum glucose (243 mg/dl), potassium (2.4

mmol/l), total bilirubin (1.59 mg/dl), γ -glutamyl transferase (73 U/l), and prothrombin time (1.37 international normalised ratio, normal values from 1.00 to 1.27). Examination of CSF one day after admission showed a raised CSF/serum albumin ratio (12.5), but a normal cell count (no malignant cells were detected) and glucose concentration; fluid was sterile on culture. Oligoclonal IgG bands were absent in the CSF. A cranial CT on admission as well as bilateral carotid angiography three days after admission were normal. Five days after admission her mental state deteriorated. She was intubated and transferred to the neurology intensive care unit. On admission there she was comatose without reaction to painful stimuli. Oculocephalic responses were absent. The isocoric pupils had slight bilateral reaction to light. Corneal reflexes were symmetrically present. An EEG showed diffuse slowing. She had hypotension requiring fluid administration, dopamine, and noradrenaline. She had a fever (39°C) and a raised C-reactive protein concentration (13.8 mg/dl); antibiotic treatment (imipenem plus erythromycin) was initiated. Repeat cranial CT was normal. Twenty four hours after admission at the intensive care unit she acutely developed bilateral dilated areactive pupils. Immediate CT showed severe intraventricular haemorrhage (figure, A). Coagulation studies (prothrombin time, partial thromboplastin time, platelet count) determined on the same day as well as the day before intraventricular haemorrhage were normal. The patient had no clinical signs of cutaneous or mucous bleeding. Despite immediate insertion of bilateral intraventricular drains the patient died 14 hours later.

At necropsy the brain weighed 1440 g and showed some arteriosclerosis of the great arteries at the base of the brain. An aneurysm was not found in the circle of Willis. Coronal sections showed pronounced haemorrhages at the walls of the third ventricle bilateral, which extended into the third ventricle, the aqueduct, and the floor of the fourth ventricle (figure, B, C). There was destruction of the mamillary bodies by haemorrhage. In addition to petechial haemorrhage, microscopy showed prominent and dilated capillaries, reactive astrocytes in the periventricular regions around the third and fourth ventricles and aqueduct, and mild neuronal loss.

The clinical diagnosis of Wernicke's encephalopathy is often overlooked¹ and was not suspected in our non-alcoholic patient during her lifetime. Her mental abnormalities had aroused clinical suspicion of carcinomatous meningitis, paraneoplastic disorder, cerebral vasculitis, or sinus thrombosis. A recent necropsy study showed that 80% of patients with the Wernicke-Korsakoff syndrome were not diagnosed during life (Harper *et al*, 1986, cited in Naidoo *et al*¹). Apart from patients with a history of chronic alcoholism, Wernicke's encephalopathy can be found in other medical settings—for example, malnutrition, prolonged intravenous feeding, cancer, gastric plication, and acquired immunodeficiency syndrome.^{1,2} The extensive abdominal surgery and vomiting before admission may have led to decreased food uptake and thiamine deficiency in our patient. Parenteral nutrition in the intensive care unit probably aggravated Wernicke's encephalopathy.

Neuropathological studies in patients with Wernicke's encephalopathy have shown symmetric lesions in the paraventricular regions of the thalamus and hypothalamus, in the mamillary bodies, periaqueductal region of the midbrain, floor of the fourth ventricle, and midline structures of the cerebellum.² Histologically, the acute lesions were found in and around blood vessels. Hypertrophic endothelial cells, demyelination, loss of neuropil, proliferation of astrocytic and microglial cells, and relative preservation of neurons have been reported in neuropathological studies. Periventricular haemorrhages, usually petechial in size, may be found in up to 20% of cases. Two patients were reported to have died of extensive haemorrhagic brainstem lesions detected on necropsy.³

Wernicke's encephalopathy remains a clinical diagnosis, because of the insensitivity of neuroimaging in this setting. Initial CT in our patient was normal. Haemorrhages due to Wernicke's encephalopathy detected on CT or MRI are seldom reported in the medical literature. In one report scattered haemorrhages in the thalami and posterior diencephalon in a patient with Wernicke-Korsakoff syndrome were shown by CT.⁴ In a case report a small haemorrhagic lesion adjacent to the body of the lateral ventricle was discovered on MRI.⁵ The severe intraventricular haemorrhage due to Wernicke's encephalopathy as seen in our patient raises the question of whether spontaneous bleeding of Wernicke's encephalopathy was accentuated by an associated coagulopathy. At the time of ventricular haemorrhage the data on clotting studies were normal. Moreover, the patient had not received antiplatelet agents.

HANS-WALTER PFISTER
FRIEDRICH VON ROSEN
Department of Neurology
KARL BISE
Institute for Neuropathology,
Ludwig-Maximilians-University of Munich,
Germany

Correspondence to: Professor Hans-Walter Pfister, Ludwig-Maximilians-University, Department of Neurology, Klinikum Großhadern, Marchioninistraße 15, 81377 Munich, Germany.

- 1 Naidoo DP, Bramdev A, Cooper K. Wernicke's encephalopathy and alcohol-related disease. *Postgrad Med J* 1991;67:978-81.
- 2 Victor M, Adams RD, Collins GH. *The Wernicke-Korsakoff syndrome and related disorders due to alcoholism and malnutrition*. 2nd ed. Philadelphia; Davis, 1989:1-117.
- 3 Harper C. Wernicke's encephalopathy: a more common disease than realised. A neuropathological study of 51 cases. *J Neurol Neurosurg Psychiatry* 1979;42:226-31.
- 4 Roche SW, Lane RJM, Wade JPH. Thalamic hemorrhages in Wernicke-Korsakoff syndrome demonstrated by computed tomography. *Ann Neurol* 1988;23:312.
- 5 Schroth G, Wichmann W, Valavanis A. Blood-brain barrier disruption in acute Wernicke encephalopathy: MR findings. *J Comput Assist Tomogr* 1991;15:1059-61.

Neuromyotonia in association with malignant hyperpyrexia

We report a case of neuromyotonia in a patient with malignant hyperpyrexia.

The patient, a 19 year old woman, has had several discrete episodes of muscular stiffness over her lifetime and several years of twitching in the hand and calf muscle. Episodes of calf muscle contracture and pain had occurred from the age of 5 with two severe episodes at the ages of 5 and 16.