5 Karlson EW, Sudarsky L, Ruderman E, Pierson S, Scott M, Helfgott. Treatment of stiff-man syndrome with intravenous immunoglobulin. *Arthritis Rheum* 1994;37: 915-8.

Increase of flexor reflex latency in patients with amyotrophic lateral sclerosis treated with riluzole

Recently, riluzole has been reported to increase life expectancy in patients with amyotrophic lateral sclerosis.¹ Pharmacologically, riluzole is an inhibitor of glutamate release and a non-competitive antagonist at N-methyl-D-aspartate receptors.² Glutamate antagonists are also undergoing clinical trials for several other diseases. It is known that the H reflex and flexor reflexes in experimental animals are mediated by different subtypes of ionotropic glutamate receptors³; the flexor reflex by NMDA receptors and the H reflex by non-NMDA receptors. Therefore, spinal reflexes may provide an opportunity to investigate glutamatergic neurotransmission in humans in vivo. We investigated whether riluzole differentially alters the H reflex and flexor reflexes in patients with amyotrophic lateral sclerosis treated with the drug. From the natural course of the disease it is known that the density of the non-NMDA binding sites increases in the spinal cords of patients with amyotrophic lateral sclerosis.⁴ We therefore expected that treatment with riluzole would maintain the latency of the H reflex and increase the latency of the flexor reflexes.

The study was approved by the Ethikkommission of the Humboldt-University.

The H reflex (recorded from M soleus) and the flexor reflex (recorded from M tibialis anterior) were investigated in 15 controls (nine men, six women, mean age 25 years) and 10 patients with amyotrophic lateral sclerosis, at onset and after three months of treatment with 50 mg riluzole twice a day (four men, six women, age range 35-75 years; less than 30 months since the onset of clinical symptoms). The H reflex was investigated in a sitting position⁵ with stimulation of the nerve in the popliteal fossa. The flexor reflex was elicited in a sitting position with the foot mildly dorsally flexed. Stimulation was performed at the plantar aspect of the foot (20 ms duration, 50 Hz, 50 mA). The stimulus was recog-

nised as a sharp burning pain but was tolerated by all patients and controls. The differential electrode was placed 10 cm below the patella ligament, the indifferent 3 cm distal over the tibial bone. In controls, the mean latency of the H reflex was 29.2 (SD 2.0) ms and of the flexor reflex 80.1 (SD 7.1) ms. At the onset of treatment with riluzole, the mean latency for the H reflex in patients with amyotrophic lateral sclerosis was 31.0 (SD 3.3) ms. After three months of treatment with riluzole, the latency was unchanged at 30.4 (SD 3.0) ms. The respective values for the flexor reflexes were 72.5 (SD 6.6) ms at onset and 121.1 (SD 17.6) ms ($P < 0.05$; fig 1) after three months of treatment with riluzole.

The latencies of the H reflex in controls and untreated patients with amyotrophic lateral sclerosis are consistent with the medical literature. The latency and pattern of the flexor reflex is similar to the report from which the method was adapted.⁵ Our results show that the H reflex and the flexor reflex are differentially affected in patients with amyotrophic lateral sclerosis treated with riluzole. The latency of the H reflex did not change in patients treated with riluzole, whereas the latency of the flexor reflex increased. This is consistent with the known pharmacological properties of riluzole as a non-competitive antagonist at NMDA receptors.²

We conclude that spinal reflexes can be used to investigate the differential modulation of glutamatergic neurotransmission in situ in humans. Possibly, these diagnostic tests can be used to evaluate pharmacological therapies with glutamate antagonists.

M W RIEPE
G KLAPPENBACH
A C LUDOLPH

Department of Neurology, Humboldt-University,
Berlin

Correspondence to: Dr Matthias W Riepe, Department of Neurology, University of Ulm, Steinhövelstr. 9, 89075 Ulm, Germany.

1 Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V, for the amyotrophic lateral sclerosis/riluzole study group-II. A dose ranging study of riluzole in amyotrophic lateral sclerosis. *Lancet* 1996;347:1425-31.

2 Debono MW, Le Guern J, Canton T, Doble A, Pradier L. Inhibition by riluzole of electrophysiological responses mediated by rat kainate and NMDA receptors expressed in *Xenopus* oocytes. *Eur J Pharmacol* 1993; 235:283-9.

3 Turski L, Bressler K, Klockgether T, Stephens

DN. Differential effects of the excitatory amino acid antagonists, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and 3-($\pm$)-2-carboxypiperazin-4-yl-propyl-1-phosphonic acid (CPP), on spinal reflex activity in mice. *Neurosci Lett* 1990;113:66-71.

4 Shaw PJ, Chinnery RM, Ince PG. Non-NMDA receptors in motor neuron disease (MND): a quantitative autoradiographic study in spinal cord and motor cortex using ³H CNQX and ³H kainate. *Brain Res* 1994; 655:186-94.

5 Hugon M. Proprioceptive reflexes and the H-reflex. In: Desmedt JE ed. *New developments in electromyography and clinical neurophysiology*. Basel: Karger, 1973:277-93.

Progressive multifocal leucoencephalopathy treated with cytosine arabinoside: 12 year follow up and postmortem findings

This patient was the subject of a previous report in 1975.¹ We now report follow up until her death in 1985 and the postmortem examination.

Sarcoidosis was first diagnosed in 1959, at the age of 38 years, after uveoparotitis and a left facial palsy. She had iritis in 1965 and evidence of pulmonary sarcoidosis in 1966. Treatment was then started with prednisolone (7.5 mg daily). In 1972 she had mumps in September and in October difficulty with the use of her right hand which slowly progressed to a right hemiparesis, associated with facial weakness and dysphasia. A diagnosis of progressive multifocal leucoencephalopathy was confirmed by cerebral biopsy and viral culture. Within a few weeks of starting treatment with cytosine arabinoside (2 mg/kg) in September 1973 definite improvement was seen. She returned to work as a nursing tutor in November 1973. By February 1975, at the time of the first report,¹ she was continuing with five day courses of cytosine arabinoside separated by intervals of three weeks, without complications. She continued to improve and there was at that time no evidence of speech disturbance. She had minimal right sided facial weakness, moderate spastic weakness of the right arm with quite dense cortical motor deficit in the hand, and obvious cerebellar ataxia involving the right arm and hand.

In May 1975 she developed intermittent lower abdominal colic with abdominal distension and tenderness associated with nausea, flatulence, and borborygmi. A barium meal and follow through showed uniformly dilated loops of bowel and coarse oedematous mucosal folds with an abnormal mucosal pattern. Further investigations showed malabsorption of B12, iron, and folate. Biopsy showed subtotal villus atrophy. In October 1975 further gastroenterological investigations gave similar results. These gastrointestinal abnormalities have not been described with cytosine arabinoside. Gluten sensitive enteropathy was confirmed by a response to a gluten free diet with considerable sustained improvement, apart from very occasional inadvertent gluten exposure, usually from gluten filler in tablets.

She had visual migrainous equivalents for many years, which only rarely proceeded to headache. Some of these attacks were associated with numbness of one or other hand, usually the right hand. In April 1976 she was having increasing attacks of migraine and found that if the right hand was affected, she became quite obviously dysphasic for an hour or more. If the numbness

Flexor reflexes in one patient at onset of treatment and after three months of treatment with riluzole (two recordings superimposed).

Figure 1 (A) Old biopsy site (arrowhead) with a scar in the underlying white matter. A separate well demarcated grey lesion is present in the adjacent white matter (arrow). (B) Two irregular grey lesions (arrows) in the right parietal lobe, including a very small one impinging on the cortex.

affected the left hand, then she had some dysarthria. The association of the lateralisation of a migrainous aura with aphasia if her right hand was affected and with dysarthria if her left hand was affected is predictable, if extremely unusual, and has not been previously described.

In December 1977 she developed herpes zoster affecting the right sacral 3–5 segments. She continued to produce crops of cutaneous sarcoid. In July 1982 there was deterioration in her mental state due to inappropriate ADH secretion requiring fluid restriction. In March 1984 she developed avascular necrosis of the left shoulder due to steroids and in January 1985 she had a left shoulder prosthesis. In September 1985 she developed a febrile illness with rapid deterioration, she lapsed into coma and died.

A necropsy carried out by Dr WL Brander showed that the cause of death was acute pyelonephritis with septicaemia. No evidence of pulmonary sarcoidosis was found. The brain weighed 1272 g. The leptomeninges over the frontal convexity were mildly opaque and thickened. There was a small old contusion in the orbital surface of the right frontal lobe. The old biopsy site in the left hemisphere was marked by a 1.5 cm diameter defect with underlying scarring (fig 1A). The lateral ventricles, including the temporal horns, were enlarged, as was the

third ventricle. In the white matter, there were numerous irregular grey, slightly depressed lesions in both hemispheres (fig 1B), the largest measuring 1.8 × 1 cm. In the left frontal lobe the lesions were shrunken and cavitated.

The corpus callosum and periventricular regions were well preserved. Similar lesions were also seen in the right putamen and left thalamus. The cortex was relatively well preserved. The cerebellum, brainstem, and spinal cord appeared normal. Histological examination showed that there were large and small poorly demarcated pale lesions in the white matter of burnt out progressive multifocal leucoencephalopathy. They were sparsely cellular, containing astrocytes, some with large bizarre nuclei containing PAS positive inclusions (fig 2A). However, immunocytochemistry for JC virus failed to reveal the Papova virus antigen. Sections from the patient's earlier biopsy demonstrated the presence of the viral antigen when stained with the same antibody. No viral particles were seen in postmortem tissue taken for electron microscopy as had been found in the biopsy.¹ The lesions involving the deep grey matter looked similar.

In addition there was widespread meningovascular sarcoidosis (fig 2B). Loose granulomata composed of epithelioid cells, lymphocytes, plasma cells, and multinucleated giant cells were present in the leptomeninges and in the walls of meningeal veins and arteries. The inflammation was more severe in the region of the biopsy site and extended into the underlying scarred brain. In the cerebellum only, there was patchy cortical scarring related to the meningeal sarcoid. There was no degeneration of the long tracts of the brainstem and spinal cord. Re-examination of the earlier biopsy showed mildly thickened leptomeninges but no evidence of sarcoidosis.

Progressive multifocal leucoencephalopathy typically has a fatal outcome, usually within six months.² Rare exceptions include a patient also with coeliac disease, who died 10 years after the onset of the illness,³ and another with lymphosarcoma and progressive multifocal leucoencephalopathy for five years who seemed to have periods of clinical remission.⁴

There has been considerable increase in interest in the management of patients with this condition in recent years because of the AIDS epidemic. The response to cytosine arabinoside is usually disappointing. Most reported patients have only received one or two courses of five days. This patient was given an unusual drug regime with five day courses of intravenous cytosine arabinoside at three weekly intervals for a year and the intervals were slowly extended to two months over a second year and to three months for the third year. She had her last course of treatment in May 1978, just over three years from the first treatment. This programme was devised because it did not seem likely that cytarabine would eliminate the virus completely from the nervous system and her immunosuppressed state persisted throughout this time.

The pathological evidence indicates cure from progressive multifocal leucoencephalopathy, which has not been claimed before. Cytosine arabinoside seems to have effected this cure, as her condition deteriorated progressively until treatment was started and improvement occurred soon afterwards.

Figure 2 (A) Large oligodendrocyte nucleus with a PAS positive inclusion (arrow). PAS originally × 800. (B) Ill demarcated granulomata with multinucleated giant cells (arrows) in the leptomeninges. Part of the wall of a vein (arrowhead) is involved. Haematoxylin and eosin originally × 126.

We are grateful to Dr WL Brander, who kindly sent the brain to us for examination and to Dr Herbert Budka who performed the immunocytopathology.

MD O'BRIEN
Department of Neurology,
Guy's Hospital, London

M HONAVAR
Department of Neuropathology,
Institute of Psychiatry, Denmark Hill, London

Correspondence to: Dr MD O'Brien, Department of Neurology, Guy's Hospital, London SE1 9RT, UK.

- 1 Marriott PJ, O'Brien MD, Mackenzie ICK, Janota I. Progressive multifocal leucoencephalopathy: remission with cytarabine. *J Neurol Neurosurg Psychiatry* 1975;38:205–9.
- 2 Esiri MM, Kennedy PGE. In: Hume Adams J, Duchon LW, eds. *Virus disease, in Greenfield's neuropathology*. 5th ed. London: Edward Arnold, 1992:335–9.
- 3 Kepes JJ, Chou SM, Price LW. Progressive multifocal leucoencephalopathy with 10 year survival in a patient with non tropical sprue. *Neurology* 1975;25:1006–12.
- 4 Hedley-Whyte JE, Smith BP, Tyler RH, Peterson WP. Multifocal leucoencephalopathy with remission and five year survival. *J Neuropathol Exp Neurol* 1966;25:107–16.

MATTERS ARISING

Brain and spinal cord MRI in motor neuron disease

In your September issue, Thorpe *et al*¹ describe their MRI findings in 11 patients with motor neuron disease. They found symmetric areas of high signal intensity on T2 weighted images within the corticospinal tracts, as previously reported by other investigators. We² reported a case of amyotrophic lateral sclerosis with further high signal intensity in fibres of the corpus callosum on proton density and T2 weighted images, closely matching findings of earlier pathological reports.³ We would be interested to know if Thorpe *et al* found similar callosal signal abnormalities in some of their patients. These findings would enhance the diagnostic role of MRI in patients with suspected motor neuron disease, as suggested by the authors.

MICHEL VAN ZANDIJCKE
Department of Neurology
JAN CASSELMAN
Department of Medical Imaging
AZ St-Jan,
Ruddershove 10,
B-8000 Brugge, Belgium.

Correspondence to: Dr M V Zandijcke.

- 1 Thorpe JW, Moseley IF, Hawkes CH, *et al*. Brain and spinal MRI in motor neuron disease. *J Neurol Neurosurg Psychiatry* 1996;61:314–7.
- 2 Van Zandijcke M, Casselman J. Involvement of corpus callosum in amyotrophic lateral sclerosis shown by MRI. *Neuroradiology* 1995;37:287–8.
- 3 Brownell B, Oppenheimer DR, Hughes JT. The central nervous system in motor neuron disease. *J Neurol Neurosurg Psychiatry* 1970;33:338–57.

Thorpe *et al* reply:

We thank Van Zandijcke and Casselman for bringing their case to our attention and confirm their findings. We reviewed our axial proton density and T2 weighted images and found high signal in the corpus callosum in