Serum cholinesterase activity was absent until day 20. He developed severe organophosphorus intoxication with coma, cholinergic crisis, and complete paralysis (intermediate syndrome). Mechanical ventilation was necessary for 33 days while he gradually recovered. During this time, repetitive nerve stimulation of the median nerve at frequencies of 2 to 50 Hz showed a prominent decremental response of the thenar compound muscle action potential (CMAP) until day 14. This decremental response then gradually subsided and disappeared by day 27.

He subsequently became alert and complained of numbness and weakness in his feet and hands at four weeks after the acute intoxication. Clinical examination showed signs of severe, symmetrical, distal, sensorimotor polyneuropathy. Findings included mild weakness of hand muscles, and paralysis of all distal leg and foot muscles with severe muscle atrophy. Deep tendon reflexes were absent in the legs although they had been present earlier, at the time of the acute severe paralysis. No plantar reflexes were present. Vibration sense was diminished mildly at the ankles. He was unable to stand or walk. CSF examination at this time was normal. Peroneal nerve stimulation at the fibular head and the ankle showed no CMAP from the extensor digitorum brevis. Nerve conduction velocity of the median nerve was normal (52 m/s; CMAP amplitude 5 mV). Repetitive nerve stimulation studies at this time were normal. EMG of both anterior tibial muscles showed profuse fibrillations without voluntary motor unit potentials present. Thenar EMG exhibited only few fasciculations with reduced recruitment. During the next five weeks, muscle strength gradually recovered, more completely in the hands than in the feet. Eventually he was able to walk without assistance, but distal weakness persisted in the legs. No pyramidal tract signs evolved.

In our patient, the intoxication with a pure formulation of an ethyl-parathion pesticide induced a severe axonal polyneuropathy which was clinically apparent four weeks after intoxication. Clinical and electrophysiological manifestations included distal extremity weakness, severe in the legs, associated with severe muscle atrophy as well as loss of reflexes in the legs, and nerve conduction velocity and EMG changes indicative of severe axonal loss and denervation. These findings are incompatible with the more acute weakness of the intermediate syndrome, occurring much earlier in the course of organophosphorus intoxication, and associated only with the electrophysiological features of neuromuscular junction blockade. The electrophysiological findings of this blockade had subsided and supervening axonal damage was confirmed by EMG and nerve conduction studies.

This case is similar to that reported by de Jager, *et al*³ in whom clinical and neurophysiological findings demonstrated a delayed neuropathy following severe ethyl-parathion intoxication. This compound is not known to irreversibly inhibit the neuropathy target esterase and, in adult hens, no delayed neurotoxicity is seen.⁶ The reason for the neuropathy in these patients therefore remains uncertain. It has been argued that both the chemical structure of the organophosphorus compound and the degree and duration of intoxication contribute to the irreversible inhibition of the

esterase.² All delayed neuropathies following intoxication with compounds not normally neurotoxic—for example, ethyl-parathion and carbamates, have been seen after very severe or prolonged intoxications. This has occurred in only a few cases to date.³⁻⁵ Ethyl-parathion intoxication as severe as in our case is unusual, and many such severely intoxicated patients die before the time interval for delayed neurotoxicity has been reached.

This patient was the only one of 36 suicidal organophosphorus poisonings, admitted to the Hospital of the University of Mainz since 1986, who developed a delayed polyneuropathy. He had by far the most severe intoxication in this series, because it was not possible to perform gastric lavage. High ethyl-parathion serum levels were documented for eight days and serum cholinesterase was absent for 20 days. This is in contrast to our other patients in whom serum organophosphorus levels persisted for up to three days only; serum cholinesterase levels were absent for up to six days only. This report confirms the view that a delayed polyneuropathy may occur in humans with organophosphorus compounds that are not usually neurotoxic, if the intoxication is severe and sufficiently prolonged. The absence of corticospinal tract signs is noteworthy and is similar to previous reports of the delayed polyneuropathy resulting from ethyl-parathion and carbamates. This suggests that the pathogenesis of the polyneuropathy differs in these cases from the more classical delayed neurotoxicity, that is, irreversible inhibition of neuropathy target esterase.

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Reverse ocular bobbing due to combined phenothiazine and benzodiazepine poisoning

Observation of spontaneous eye movements may be of considerable value in the diagnosis of the unconscious patient.¹ Slow roving

eye movements, for example, imply a disorder sparing the brainstem oculomotor circuitry, whilst ocular bobbing (that is, rapid conjugate downward movement of the eyes followed by a slow return to the primary position, typically associated with a loss of horizontal eye movements) is usually due to structural pathology affecting the pons although cases due to metabolic or toxic encephalopathy have been described.²⁻³ Reverse ocular bobbing (that is, rapid conjugate upward movement followed by slow return to the primary position) is generally a less reliable guide to the localisation of pathology.^{1,4} We describe two cases where reverse ocular bobbing occurred in coma due to covert combined phenothiazine and benzodiazepine poisoning.

Patient 1, a 14 year old schoolboy, was brought to a casualty department after his parents had found him drowsy and dysarthric with difficulty in walking; they said he had been unhappy because his brother had recently had a relapse of schizophrenia but felt that he did not have access to his brother's drugs. On arrival he was stuporose but opened his eyes, grunted and moved his limbs semi-purposefully to a painful stimulus; there were no focal neurological signs. Shortly afterwards he had a series of episodes of involuntary limb and neck extension and unresponsiveness lasting several minutes. These were thought to be epileptic seizures and were treated with boluses of intravenous diazepam to a total dose of 20 mg. In retrospect, it is clear that they were dystonic spasms. He became deeply unconscious and unresponsive to pain. Encephalitis was suspected and he had CT brain scanning and examination of CSF by lumbar puncture; both were normal and he was transferred to this unit. He had mild cogwheel rigidity in the right arm and episodes of spontaneous reverse ocular bobbing with a frequency of 1-2 Hz which lasted one to two minutes and occurred several times per hour. A search of his clothing revealed a suicide note; his parents later reported that sixty 50 mg tablets (that is, 3 g) of chlorpromazine were missing from his brother's supplies. He regained consciousness over the next 18 hours; he then experienced a series of typical oculogyric crises with compulsive upwards deviation of both eyes, which responded to anticholinergic therapy. He was transferred for psychiatric treatment.

Patient 2, a 26 year old woman, whose occupation afforded access to a variety of medical drugs, was brought to a casualty department in a stuporose state. She described a recent mild head injury and denied ingestion of drugs other than therapeutic doses of aspirin. Over the next six hours her conscious level deteriorated, with no responses to pain and slow shallow respiration. Pupillary, vestibulo-ocular, corneal and gag reflexes were preserved. Routine blood tests were normal; her blood salicylate level was 90 mg/dl. Urgent CT brain scan followed by CSF examination by lumbar puncture were normal and she was transferred to this unit.

Examination remained unchanged except for spontaneous reverse ocular bobbing with a frequency of 1-2 Hz that occurred in bursts lasting several seconds every few minutes; these bursts could be observed through her closed eyelids and were not affected by opening her eyelids. Toxicological testing subsequently revealed

the presence of prochlorperazine and an unspecified benzodiazepine in her urine; a packet of buccal prochlorperazine (Buccastem) from which 12 tablets (36 mg) had been removed was later found in her car but the source of the benzodiazepine was not identified. The abnormal eye movements resolved after twelve hours; she regained consciousness over 36 hours, declined psychiatric assistance and discharged herself from the ward.

In an unconscious patient the presence of ocular bobbing should raise the possibility of structural pathology in or around the pons. As these cases illustrate, however, other forms of spontaneous vertical eye movement disorder may be due to toxic or metabolic encephalopathies and ideally consideration should be given to such causes before embarking upon invasive investigation. Self-poisoning is by far the commonest cause of coma in patients presenting to casualty departments, but can often only be diagnosed on the basis of circumstantial evidence and subsequent toxicological screening.

Both of these patients were exposed to the unusual combination of phenothiazines and benzodiazepines. The pharmacological basis of the eye movements is not clear. It is possible that they represent a form frustre of oculogyric crisis produced by phenothiazines and modified by benzodiazepines. Typical phenothiazine-related oculogyric crises cause sustained upwards deviation of the eyes (often with a lateral component) associated with obsessional thoughts and a feeling of unease.⁵ One of the present patients developed these typical episodes on regaining consciousness. Whilst unconscious, both patients had episodes of unsustained rapid conjugate upwards deviation of the eyes, interspersed by slower drifts back to the primary position. Benzodiazepines have complex actions⁶ on the brainstem circuits which may be responsible for the generation and maintenance of vertical gaze both under normal circumstances and during oculogyric crises,^{1,5} and have been used to treat the latter.⁷ If the reverse ocular bobbing is indeed a modified form of oculogyric crisis one would expect it to be abolished by intravenous anticholinergic drugs, which almost always abolish typical oculogyric crises. This was not attempted during the episodes of reverse ocular bobbing here but, if validated in future cases, might form the basis of a simple bedside test for combined phenothiazine and benzodiazepine poisoning.

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MATTERS ARISING

Treatment of lower urinary tract dysfunction in patients with multiple sclerosis

In this paper¹ we concluded that simple treatments could improve the bladder symptoms in multiple sclerosis, but before embarking on therapy it is important to detect incomplete bladder emptying which can exacerbate detrusor hyperreflexia. The paper was the result of discussions by a group of urologists and neurologists convened in March 1991 by the European Study Group of SUDIMS (Sexual and Urological Disorders in Multiple Sclerosis).

Although a consensus was reached then on which therapies are effective and desirable, there was no agreement about what pretreatment investigations were necessary or who should arrange them. At a second SUDIMS meeting in Copenhagen in May 1992 the subject of minimal investigations was again discussed. Again the views of the neurologists and urologists remained essentially irreconcilable but there was agreement on those investigations a neurologist might reasonably arrange for a patient with MS and bladder symptoms. These are: 1) exclude urinary tract infection; 2) detect incomplete bladder emptying.

Anticholinergic medication alone is unlikely to correct symptoms of urgency and frequency in the presence of either of these two disorders. The neurologist should arrange and follow up these investigations if possible. Urological advice should be sought if the patient does not get better or suffers recurrent urinary tract infections.

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The use of multiple anti-dystrophin antibodies in Duchenne and Becker muscular dystrophy

A recent paper by Muntoni *et al*¹ describes the use of multiple anti-dystrophin antibodies in Duchenne and Becker muscular dystrophy. I was particularly interested in the discordance in staining between the various antibodies in the very mild or preclinical Becker phenotypes. Presumably this is explained by small in-frame deletions that affect antigenic regions of dystrophin identified by one antibody and not the other. Although Western blot analysis was carried out, and said to confirm the immunofluorescence results, no data are shown.

The question I would like to put to the authors is whether dystrophin (presumably of slightly reduced molecular weight) from such asymptomatic or mildly affected

Becker patients could be distinguished from normal dystrophin on Western blot analysis using an anti-dystrophin antibody that gives normal immunocytochemistry pattern. If this were the case, then it would obviate the need to use multiple antibodies to avoid underdiagnosing the mild or asymptomatic Becker phenotypes.

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Muntoni *et al* reply:

Dr Kyriakides's observation gives me the opportunity to clarify my view on this important matter. The underlying question asked is: is there a single, preferred technique for detecting dystrophin abnormalities and are there occasions when other techniques should be considered instead?

Although our study¹ was not specifically designed to address this particular point, I have reached my conclusion on the basis of the following observations:

A) Western blot *qualitative and quantitative* abnormalities: these were observed in the great majority of the patients we have analysed (90%), including the ones with very mild or preclinical Becker muscular dystrophy (BMD) phenotypes. In particular, two preclinical BMD patients showed a slightly reduced molecular weight protein of slightly lower abundance on Western blot analysis. Immunocytochemical analysis with multiple anti-dystrophin antibodies was judged to be abnormal before the knowledge of the immunoblot result.

B) Western blot *quantitative* abnormality: this was observed in patient BMD 17,¹ a boy still asymptomatic at the age of 10. There was also discordance in staining between the various anti-dystrophin antibodies.

It thus appears that while most BMD patients have an abnormal molecular weight dystrophin on Western blot, a few (in the very mild end of the spectrum of dystrophinopathies) will only have a reduced amount of a normal molecular weight protein. We have been able to pick up immunocytochemical abnormalities in these patients, but as concluded in our paper, a normal result with immunocytochemistry should not stop one from doing a Western blot, if a dystrophinopathy is still suspected. On the other hand, precise quantitation of dystrophin present on a Western blot can be rather difficult, especially in cases where it is close to normal. Few laboratories around the world routinely carry out dystrophin quantitation corrected for the myosin content of the muscle sample.²

Western blot analysis is a technically demanding, expensive and time consuming technique (taking a minimum of two and a half days). Its use cannot therefore be easily justified for individual samples. On the other hand, immunocytochemical analysis with a panel of anti-dystrophin antibodies can be done on individual samples in a couple of hours by a technician with routine histochemical skills.

Another important piece of information that can be derived from immunocytochemical analysis relates to detecting the location of genomic or transcription abnormalities.