Table Nerve Conduction Studies

	Day 2	Day 3	Day 7	Normal*
Mean serum K (mmol/l)	1.9	3.2	4.0	3.5–5.0
Sensory action potential amplitude (μ V)/peak latency (ms)				
Right median F2-wrist	20/4.0	20/3.4	20/2.8	> 8
Right ulnar F5-wrist	12/3.8	9/2.9	12/1.9	> 7
Right sural	8/5.6	18/3.6	13/3.7	> 5
Compound muscle action potential distal/proximal stimulation (mV)				
Right median (SE APB)	1.5/0.6	4.0/3.8	NT	> 3.5
Right ulnar (SE ADM)	0.7/0.6	5.0/4.6	4.5/3.8	> 5
Right lateral popliteal (SE EDB)	1.2/1.2	0.8/0.8	1.0/0.9	> 2
F wave latency (ms)				
Right median (wrist)	35	32	NT	< 31
Right ulnar (wrist)	44	30	29	< 32
Motor conduction velocity (m/s)				
Right median (forearm)	46	49	NT	> 48
Right ulnar (forearm)	42	58	55	> 50
Right lat. popliteal	38	43	47	> 39
Distal motor latency (ms)				
Median	5.8	3.9	NT	< 4.8
Ulnar	3.5	3.2	2.4	< 3.5
Lateral popliteal	5.0	6.0	4.1	< 6.5

SAP = sensory action potential; CMAP = compound muscle action potential; APB = abductor pollicis brevis; ADM = abductor digiti minimi; EDB = extensor digitorum brevis, MCV = motor conduction velocity; DML = distal motor latency; NT = not tested.

conduction studies performed in the intensive care unit on days 2, 3, and 7. The first study showed a marked reduction in the amplitude of surface recorded compound muscle action potentials (CMAPs) to distal stimulation of the median, ulnar, and lateral popliteal nerves, with slight prolongation of distal motor latencies and delay and paucity of F waves. Motor conduction velocities were slightly reduced but sensory action potentials were of normal amplitude. Electromyography with a concentric needle electrode in the tibialis anterior revealed no spontaneous activity, but no motor units were seen under voluntary control and there was only a small visible muscle twitch to nerve stimulation (the patient was mildly sedated for ventilation, but neuromuscular blocking drugs were not administered). An electrocardiogram on admission was normal.

Initial treatment consisted of intravenous potassium and fluids with parenteral antibiotics. As serum potassium rose, her strength improved and leg reflexes returned. Between days 2 and 3, proximal muscle power increased from grade 2/5 to 4/5, and distal power increased from grade 3/5 to 4+/5 on the MRC scale. This was associated with a commensurate improvement in the size of CMAPs, and a decrease in distal and F wave latencies to normal as serum potassium levels rose from 1.9 to 3.2 mmol/l (table 1). A repeat EMG of upper and lower limb muscles on day 3 showed a severely reduced interference pattern with motor units firing irregularly at 10–20 Hz at 1–2 mV. Occasional units were of spiky configuration but most were of normal form and amplitude.

The metabolic acidosis and polyuria persisted and potassium remained at 3.3 mmol/l, so parenteral bicarbonate was given, with 5% dextrose and spironolactone for secondary hyperaldosteronism. After three days she was given oral bicarbonate (3.6 g NaHCO₃ and 17 g KHCO₃). This therapy was associated with a progressive improvement in her condition and seven days after admission her muscle power and respiratory function had fully recovered. Nerve conduction studies at this stage had also returned to normal. Her electrolytes and polyuria gradually improved and by discharge her potassium was 4.2 mmol/l, creatinine 176 μ mol/l, and she was passing three

litres of urine a day.

The most striking initial electrophysiological abnormality was a severe and generalised reduction in CMAP amplitudes; this, in association with modest and mainly distal slowing of motor and sensory nerve conduction and some F wave latency prolongation, was compatible with, although not specific for, the acute phase of predominantly distal Guillain-Barré syndrome. The rapid recovery of CMAP amplitudes in association with the resolution of hypokalaemia and improved muscle power, however, suggests that the low potassium was responsible for the clinical and electrophysiological abnormalities. The recognised electrophysiological features of hypokalaemia, as seen in periodic paralysis, are related to muscle membrane inexcitability^{1,2} rather than nerve involvement.

Nevertheless, the exact pathophysiological mechanism of muscle weakness in these conditions is not well established; serum potassium concentration is not consistently related to the occurrence or degree of weakness, and electromyography late in the course of hypokalaemic periodic paralysis may show both neurogenic and myopathic features.³ In the present case, the abnormalities of motor conduction and electromyography could be explained by inexcitability of muscle fibres, especially those supplied by large, fast conducting myelinated nerve fibres. Although temperature effects may have contributed to the prolonged distal latencies in the initial intensive care unit study, cooling causes an increase in CMAP amplitude and therefore could not be responsible for the most prominent neurophysiological abnormality.⁴ Furthermore, conduction block in distal motor nerve fibres as part of Guillain-Barré syndrome would tend to decrease with cooling, rather than the reverse.

A further interesting feature of this case is the apparent differential response of skeletal and cardiac muscle to hypokalaemia, as the ECG on admission was normal. Hypometric saccades in the horizontal and vertical planes were recognised in our patient as a surprising finding for the syndrome, where ocular involvement, when present, is usually manifest as external ophthalmoplegia with slowed saccades.⁵

There have been a number of published reports of hypokalaemic weakness resem-

bling Guillain-Barré syndrome. Causes have included the periodic paralyses, barium toxicity, renal tubular acidosis, and even clay ingestion,^{2,6,7} but none have documented serial electrophysiological studies. This case reinforces the need for awareness of the effects of electrolytes, in particular potassium, calcium and magnesium, in both the clinical and electrophysiological assessment of weak patients.

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Polyneuropathy following parathion poisoning

Delayed neurotoxicity is a sequela of poisoning with certain organophosphorus compounds, and correlates with the irreversible inhibition of neuropathy target esterase (previously known as neurotoxic esterase).¹ This enzyme is widely distributed in the nervous system, but its physiological role is not yet known. In humans, the delayed axonal polyneuropathy occurs one to three weeks after intoxication and pyramidal tract signs are often present. The likelihood of organophosphorus compounds producing a delayed polyneuropathy is predicted by their ability to induce a similar syndrome in adult hens and these compounds are called 'neurotoxic'.² Recent clinical reports, however, have shown that compounds not usually effective in producing delayed neurotoxicity in adult hens may do so in humans following massive exposure.^{3–5} Because the pathophysiology in these intoxications is not yet understood, we present the clinical features of an additional case of ethyl-parathion induced delayed polyneuropathy.

A 23 year old man suffered from depression since the age of 19. He had attempted suicide on three occasions. His admission followed the ingestion of 15g of ethyl-parathion (E605 forte) and the infliction of a gunshot injury to his neck, penetrating the esophagus. Surgical treatment of this injury prevented gastric lavage. Ethyl-parathion serum levels were initially 400 ng/ml, increased to 550 ng/ml at day five and did not begin to decrease until day eight despite 10 haemoperfusions during this time.

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